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MAPPING OUR GENES
Federal Genome Projects: How Vast? How Fast?

Transcript of Workshop
"Issues of Collaboration for Human Genome Projects"

June 26, 1987

Discussions from this workshop were used in preparing OTA's final assessment report. OTA makes this transcript available for the use of readers desiring a more detailed discussion of an issue than can normally be accommodated in our final report. This transcript has not been reviewed or approved by the Technology Assessment Board. The views expressed at the workshop are those of the participants and do not necessarily reflect the views of OTA, the assessment advisory panel or the Technology Assessment Board.

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CONGRESS OF THE UNITED STATES

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OFFICE OF TECHNOLOGY ASSESSMENT

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WORKSHOP

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ISSUES OF COLLABORATION FOR HUMAN GENOME PROJECTS

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June 26, 1987

The meeting was called, pursuant to notice, at 9:00 a.m., Room 2322, Rayburn House Office Building, Washington, D.C.

PRESENT:

WILLIAM W. LOWRANCE, Ph.D., Chairman
Life Sciences & Public Policy Program
The Rockefeller University

BERNADETTE ALFORD, Ph.D.
Legal & Regulatory Affairs, Collaborative Research

GEORGE CAHILL, M.D., V.P. Scientific Training & Development, Howard Hughes Medical Institute

C. THOMAS CASKEY, M.D., Director
Institute for Molecular Genetics, Baylor

PRESENT (continued):

JAMES F. CHILDRESS, Ph.D., Dept. of Religious Studies, University of Virginia

SUSAN COZZENS, Ph.D., Dept. of Social Sciences, Illinois Institute of Technology

GEORGE GOULD, Esq., Hoffman LaRoche

GEOFF KARNY, Esq., Dickstein, Shapiro, Morin

EDWARD L. ROGERS, Esq., Foundation on Economic Trends

SUSAN ROSENFELD, Esq., Assn. of Bar of City of N.Y.

FRANK RUDDLE, M.D., Dept. of Biology, Yale University

ROBERT SMITH, Ph.D., History of Science Dept., Johns Hopkins University

ROBERT STEPHENSON, Ph.D., Director, American Type Culture Collection

CHARLES E. VAN HORN, Director, Organic Chemistry & Biotechnology, Patent and Trademark Office

LeROY WALTERS, Ph.D., Director, Center for Bioethics, Kennedy Institute of Ethics, Georgetown University

PATRICIA HOBEN
BOB COOK-DEEGAN
TERESA MYERS
DAVE GUSTON
JACQUELINE COURTEAU
FRED BERGMAN
MARK PEARSON
JACK WILLIAMS
RUTH KIRSCHSTEIN
DAVID SMITH
DAVID KINGSBURY
LAURA KUMIN
TOM DASHIELL

I-N-D-E-X

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P-R-O-C-E-E-D-I-N-G-S

9:37 a.m.

DOCTOR COOK-DEEGAN: Thank you for coming. My name is Bob Cook-Deegan, and I'm the Project Director for the OTA project on mapping the human genome.

We'll start off the session today with a few words from Lesley Russell, who is the Health Staff Person for Energy and Commerce. This is the committee that authorizes spending for the National Institutes of Health and mandates most of the health legislation in the House of Representatives.

MS. RUSSELL: Thank you.

Thank you all for coming today. I'm sorry that I won't have the opportunity to spend all of the day with you, but nobody has yet figured out how to clone me so that I can be in more than one place at any given time.

But, I think, even here on the Hill we have a sense of the excitement that is out there about the potential that the ability to sequence and to map the human genome provides to us, particularly in terms of

what that might mean in some of the sorts of biomedical treatment that may ultimately be available. It seems to me it's kind of like a new scientific adventure, something that's probably going to take a great deal of time, billions of dollars, and absorb the lives of hundreds of scientists.

I think already we have seen, on the Hill and elsewhere, decisions being made that will affect the progress that is made in this area. It doesn't really matter whether or not we have a boost to the current efforts that are going on, or whether or not the efforts proceed at their normal pace.

This sort of work raises a number of questions, all of which need to be considered. I think the financial considerations are probably the least of them, even though in these times of great stringency they are certainly issues that we need to think about. It's these questions that are raised that are the reasons why you are all here today.

My Chairman, Congressman Dingle, sends you all his best wishes. He wishes you a challenging and thought-provoking, and a successful day. The

Congress, and the Energy and Commerce Committee in particular, look forward to receiving the results of your efforts, and for myself, I hope personally that I'll have a chance to meet with you at lunch.

Thank you.

DOCTOR COOK-DEEGAN: I thought what I would do is introduce the purpose of the day as the first thing. The reason that we held this workshop today was really a -- my arm was twisted by the advisory panel of the Mapping the Human Genome Project at OTA when it became obvious at our panel meeting on the 6th of April that there were certain issues that we needed to address that we had not yet taken steps to address.

And so, we agreed that there would be a workshop. Although the exact topics covered at the workshop weren't too clear, it was obvious that legal and social issues were important, and over the process of the subsequent two months, the materials that you've gotten today were formulated.

The main purpose of the meeting today is to raise the arguments, so that we can incorporate

arguments into the final OTA report that will be out early next year. What that means is each of the issues that's listed on the discussion guide and that comes up for discussion that may not be on the discussion guide, we're going to be trying to take notes, there will be a transcription available to us, and we'll be trying to incorporate all the ideas of the disparate viewpoints of people around the table.

A second purpose is to help the Association of the Bar of the City of New York in narrowing the range of issues they have to deal with. We're trying to put together a contract with the Association of the Bar of the City of New York to address intellectual property protections as they might relate to mapping and possibly sequencing projects.

And the final purpose of today's meeting is to figure out if there are any other things that OTA needs to do, other than the things we've already got started and know about. So, the last thing I'd like today is to get some idea of what we might have to do in the next few months to patch up gaps or whatever else we need to do.

There are a couple starting assumptions for today's workshop that I think will help narrow the discussion a bit.

One, I think that for purposes of discussion today we can assume that there is lots of mapping and sequencing going on and that that will continue to be the case, that the Department of Energy and the NIH will both have projects whether they are coordinated or not. They will both have projects in this area. The National Science Foundation will be supporting some basic research and also the development of some instrumentation.

I think also, we should add the starting assumption that there will be some intellectual property protections based on current federal and state laws, particularly federal laws, and that the collaborations and interagency agreements would build on current laws.

The main issues that I think we should address today, although it could turn out that these aren't the major issues, I think the main issues should focus on information exchange that would be

particularly from the viewpoint of what prior agreements, that is, whatever dicta the federal agencies might put out to collaborators about sharing of information between collaborators about submission policies to journals, about submission of data to databases and repositories, and any interagency collaborative agreements that might be needed.

Secondarily, do we need any new federal laws? Are these technologies, or the results of these scientific efforts going to require a new look at some aspect of federal law related to either intellectual property protection or some other aspect of what will come up today.

There are a couple things I don't want to get into too much today, except as they relate to those issues of information sharing.

I don't want to get too much into how should an effort be structured, should the DOE do it, should the NIH do it, that sort of thing. I think it would be much more productive if we kind of assume that that's a separate question that has to be dealt with in a separate format.

I also don't think we should discuss too much what the scientific advisory structure or the social advisory structure should be for whatever projects go on in NSF, NIH, DOE, or any other nongovernment organizations. I think that will pull us into issues that are not germane to the collaborative arrangements.

If those issues of interagency organization and advisory structure come up during the day, one of the things that is an option for OTA is to convene a workshop very late in this year, probably October or November that would deal specifically with that that would involve the federal agencies and where we could look at what are the mechanisms for collaboration and advice.

Now, let me back up and set the context for the overall OTA report. Some of you in the room may not have been following our activities to date. We started this project at the request of the Energy and Commerce Committee in December. That's the committee in who's room we're meeting today.

The Project really grew out of the

scientific controversy that was played out in the pages of Science and Nature beginning last March or April and extending through the summer. There were several meetings last year, and out of those meetings two studies were started, one by the National Research Council and one by OTA.

The schedule for the OTA report is that we have drafted an interim memo that was sent out in April and revised and sent out in May. We will be starting our writing efforts for a first complete draft of the OTA report in the next few weeks. That will go out for review to our advisory panel in the last few days of August, the first days of September.

Our advisory panel will be meeting on the 18th of September for its second and final meeting, and then we will revise again based on an outside review and that advisory panel review and submit our findings to the oversight body for OTA, that's the Technology Assessment Board. Our report will go to them in December, and if all goes well and we can keep the report short, it should be out to the public sometime next spring.

We timed it, essentially, to dove-tail into the authorization/appropriation cycle for the fiscal year 1989 budget. The National Institutes of Health reauthorization is up next year and the Department of Energy authorization occurs every year, so most of the Agency stuff will come up in that context.

The next thing I would like to do is thank the Howard Hughes Medical Institute under the auspices of George, who has arranged to hold the lunch for this afternoon. Lunch is open to all the members of the advisory panel, those people who will doing presentations this afternoon, and a few other folks who called us in advance. That will be held in room B-369, and we'll have to make some sort of special arrangement at 12:15 to get down there. That's in this building, down in the basement.

The final thing I would like to do is introduce the other OTA staff on the Genome Project. We'll start with Patricia and then Dave and Jacqueline. Why don't you introduce yourselves, and then I'll turn it over to Bill.

DOCTOR HOBEN: I'm Patricia Hoben, and I'm

a molecular biologist working here at OTA as an analyst on the Mapping the Human Genome Project and on another project called U.S. Investment in Biotechnology.

MR. GUSTON: I'm Dave Guston. I'm with OTA for the summer as a Research Assistant. I've just graduated from Yale in the spring, and will be entering MIT for a PhD program in political science in the fall.

MS. COURTEAU: I'm Jacqueline Courteau. I just joined the OTA as a research assistant with this project. I'll be here until the completion of the project. I just graduated from Johns Hopkins in the Science Writing Program.

MS. MYERS: I'm Teresa Myers. I'm a part-time contractor with OTA and I've worked on the Alzheimer Assessment and also the Human Gene Therapy Assessment.

DOCTOR COOK-DEEGAN: And for those who are on the NRC panel or the OTA panel, there was a document that Dave wrote, his name may be a little familiar to you because he did a senior thesis on the

Mapping and Sequencing Project under the auspices of Yale and Frank Caruther was on his advisory committee. For those who haven't read it, it's wonderful.

CHAIRMAN LOWRANCE: Thank you. Well, Bob, I hope we can be useful to your overall study. I'm not sure we'll come up with answers today, but this is a very astute group of question askers, so we can at least pass on, I hope, some good questions for you in a very difficult and a very exciting endeavor.

I would ask you to look through the agenda, just so we're all thinking about how this day is going to go. We will begin with the discussion of the OTA discussion guide that was created in advance. That will get us going, then at 10:30, Susan Rosenfeld will present her conception of how the New York Bar Association will pursue its study during the summer. We'll have a brief break. We'll have a general discussion of all of the above, and then we have our lunch.

In the afternoon, then, to take a different view at it, we have five visitors from federal

agencies, our Hughes Institute and the NRC Committee, to make statements to the Committee. We can have some general discussion after that, then at 3:00, we'll move on to the issues of coordination in general, moving toward conclusion, and at 3:45 we'll ask what OTA should be doing in the next months to gather further information, let contracts to get specialized pieces of the puzzle examined, and so on.

So, that's essentially the way the day will go. Those afternoon presenters will be seated at the table in the afternoon, by the way, with five presenters. We will, at various points during the day, be willing to entertain comments or questions from the audience and I think it would be helpful if you slipped me a note or Bob a note along the way to say that you have a concern you'd like to raise and that will help us fit it into the discussion effectively.

Let's make out self-introductions around the table. It may be unfair, but let's start alphabetically.

DOCTOR ALFORD: I'm Bernadette Alford, with

Collaborative Research. I direct the legal and regulatory affairs for our company.

DOCTOR CAHILL: I'm George Cahill, with the Howard Hughes Medical Institute. I'm involved in the Genome Project we're with.

DOCTOR CASKEY: I'm Tom Caskey. I'm a Howard Hughes investigator and Chairman of the Department of Molecular Genetics at Baylor College of Medicine.

DOCTOR CHILDRESS: Jim Childress, University of Virginia Medical School in the Department of Religious Studies concentrating on biomedical ethics.

DOCTOR COZZENS: Susan Cozzens, Illinois Institute of Technology, science policy analysis.

MR. GOULD: I'm George Gould, Associate Patent Counsel at Hoffman LaRoche, majoring in biotechnology.

MR. VAN HORN: I'm Charlie Van Horn from the Patent Trademark Office, Director of Organic Chemistry and Biotechnology.

MR. KARNY: I'm Geoff Karny. I'm with the

Washington, DC, law firm of Dickstein, Shapiro, and Morin, and I practice in the biotech area, particularly in patents and regulation.

DOCTOR STEPHENSON: I'm Bob Stephenson, Director of the ATCC and Custodian of the genetic material.

DOCTOR SMITH: I'm Robert Smith of the History of Science Department at Johns Hopkins, and also the Smithsonian Institution, and I have a particular interest in the development of big science.

DOCTOR RUDDLE: I'm Frank Ruddle. I'm at Yale, in the Departments of Biology and Human Genetics and I'm also an advisor to the New Haven Human Gene Mapping Library.

DOCTOR WALTERS: I'm Leroy Walters. I'm in the Philosophy Department and in the Kennedy Institute of Ethics at Georgetown University.

MS. ROSENFELD: I'm Susan Rosenfeld. I'm an attorney and member of the Science and Law Committee of the Association of the Bar of the City of New York, on who's behalf I'm here today.

CHAIRMAN LOWRANCE: Leroy Walters does many other things, but I would point out that he is also Chairman of the full OTA study.

I'm Bill Lowrance from Rockefeller University in New York, where I direct the Life Sciences and Public Policy Program.

Any questions about the procedure of the day or agenda or basic ground rules?

Again, I urge you to think of ourselves as trying to be helpful to the OTA study, which has its own constraints, and although I'm sure we will wander outside our boundaries some, we should try to address the questions that Bob raised for us.

I'd ask you now to turn to the discussion guide and then -- it's entitled "Discussion Guide", about a four page, five page white piece. I would say that there's no need -- we aren't asked to develope either a report out of the day or consensus. We aren't going to vote on the right answers or even the right questions, but we are trying to air the issues in service of the overall study.

Now the discussion guide, which I hope

you've had a look at, raises two key questions. I think we should focus on those from the outset. They are stated at the bottom of the first page.

"Do current intellectual property protections need to be altered in light of the new technologies?" I would say that intellectual property protections can be construed quite broadly.

And, "Should there be special guidelines for any federally sponsored collaborations?" focusing on federal. There may be all kinds of other guidelines, and there's going to be what's called on the Hill, "co-mingling of moneys" in lots of different ways. So Hughes Institute, no doubt, and others will be involved in discussion of guidelines as well, but it we focus on the federal mostly, I think we will get at the crucial issues.

Bob, I wonder whether you'd say just a little about the structure of a discussion piece and how you saw this matrix of technologies and issues shaping up. That would get us into it.

DOCTOR COOK-DEEGAN: Sure. One of the things that I got back as feed-back from having this

discussion guide out was nobody knew why I'd listed the technologies, and I thought maybe I can clarify the purpose of the discussion guide.

The first purpose of it was to clarify my own thinking, to try to begin to compile a list of those technologies and the results of the research efforts that one could anticipate if federal and nonfederal efforts that have been discussed today are undertaken. So, I kind of listed those under various categories, and I think that is the core of the document. That's called, "What are the likely results of mapping and sequencing projects?"

The first section, of course, is just an introduction, and Bill has gone over some of the key questions. There are several sets of issues that I discuss in the introduction after I introduce the key questions, and they fall into, I think, three categories.

One is the kind of informal scientific kind of communication that we're all familiar with.

Another is interagency relationships.

And a third is international relationships.

There are different problems and potential solutions for each of those sets of issues, and I wanted to just try to dissect out some of the components of those. Those are listed under the Bullits in the first section, that is, starting with "Communication among collaborators within countries", and going down to "Export controls".

The export controls -- I should be a little clearer. I think most of the other things are pretty clear what I'm talking about. The export controls, we don't know what the status of that is. There is a list of technologies that is administered by the Department of Commerce and Consultation with the State Department and the Department of Defense that is handled with special care.

Certain things cannot be exported from the United States and cannot be reexported from other countries that contain certain highly technological components that might be used for military purposes by other countries. It's not clear whether any of these technologies relate to that and we've thrown a few trial balloons up in the air and have not found

out whether it matters or not yet. I don't know whether we're going to know that, but that is just a side proviso some of you might not be familiar with.

Then, as I said, I list the possible outcomes of the efforts. This ranges from hardware sequencing machines, gel runs, gel machines, things like that, to basic scientific information such as sequence data and map location of a particular gene or something like that.

There will be material repositories. In fact, those are perhaps the most important results of this, because those are the things that researchers would be using to do the basic stuff of biomedical research in making the project to develope mapping and sequencing data useful for the rest of science and medicine.

And finally, I just raised the mechanisms for intellectual property protection. Susan will deal with those in a bit more detail, but these are essentially the possible mechanisms. I guess I should have added one. We can strike off, probably, Trademarks, and add one called "Misappropriation"

that I only learned about recently. But I don't know if that's even relevant and --

PANEL MEMBER: Misappropriation?

DOCTOR COOK-DEEGAN: It's a term called "misappropriation". Geoff, you may want to --

MR. KARNY: It really comes into the context of trade secrets and trademarks.

DOCTOR COOK-DEEGAN: Okay.

MR. KARNY: It's what you do if you take somebody's mark or trade secret out --

DOCTOR COOK-DEEGAN: Okay.

So, the purpose of the discussion guide was just to give people something to start their thinking with, and to give you all something to shoot at. It, obviously, doesn't really tell you anything about what we're thinking about these issues. The purpose was really just to raise them so that we could start some sort of discussion early in the day.

CHAIRMAN LOWRANCE: Okay. You've given us something to shoot at. Let's shoot at it.

Any opening comments from members of the panel to start reacting to the paper. Has Bob

basically covered the territory in raising the questions?

DOCTOR STEPHENSON: Okay. Before we get into the issues of intellectual property, I think there are some unresolved issues here of "property" per se, namely the material with which we're dealing, the chromosomes themselves.

Some years ago, I was a project officer at the National Cancer Institute, and gave Doctor Leonard Hafley a contract to develop diploid cell strains as a generic material to try to find out, are these useful in the study of virus' in cancer? Over a period of some time, he developed cell strains, one of which, called the WI-38, became an infamous cell strain. The terms of the contract were for him to distribute this material to as many investigators as possible to find out the utility and convenience of using this material as substrates for all kinds of studies.

After I left the Cancer Institute and the project finally, as a contract, came to a close, the issue of ownership of those cell lines became a hotly

debated subject and resulted almost in the destruction of his scientific career. The NIH and its investigators never once even came to me and said, "What was the purpose of this contract and why was it let?"

They assumed, after a period of time, that this thing was almost like a national treasure. They marched in, seized the cells and so forth, and today the ATCC has them in closely guarded containers and we are informed that only on the direction of the project officer may we distribute any of the specified passage level to people at their direction for the purpose of making licensed vaccine.

Now the question is, with material like that, since this came from a fetus and since many cell lines have been derived from human sources of still-living people, who owns those cells? Because the government paid for the things to be manipulated and distributed, do they per se, then, own the material? I would doubt it.

Should the heirs of Helen Laks, for example, get royalties on the helo cell line? These

are issues that have never been decided and are currently the subject of still more controversy.

Related to that issue, if we are going to map the human genome, who's human genome are we going to map? I don't think that an assortment of chromosomes taken at random from 46 different people are going to be the same as 46 chromosomes taken from the same individual. Before we get into the issues of who is going to do what in terms of intellectual property, namely, what do we know about all this material, I think a very fundamental issue is, actually, who is going to own the material which is the subject of the research?

CHAIRMAN LOWRANCE: Key question.

Susan, we're not going to keep deferring everything to you, but there will be questions for you about just this, can one develop legal and legalistic stipulations that solve the problem by outlining conditions?

MS. ROSENFELD: I think that the problem which you raise really is an intellectual property law issue. You're correct that there has been a lot

of dispute over ownership of cell lines and other materials. I think that the question of who owns what in any particular situation really depends on a close examination of the facts in that particular case.

Obviously, one can tend to draft various types of contractual agreements to anticipate problems that would arise with respect to the use of cell lines and other kinds of materials, however, it is a relatively controversial area and a new area. Although one can do the best that one can in terms of trying to develop protections in advance, it's not impossible that ultimately, as a result of court decisions and other kinds of changes, the protections one thought one had in the beginning of the project might not turn out to be all that one had hoped because of unanticipated changes.

But I think that the issues that you raise are very valid and could certainly be something to be explored further in the work that the Association might do.

CHAIRMAN LOWRANCE: I think one of the

questions is, what's different about the human genome material from the other cases that you raised as well. Those were hard enough to deal with, maybe because we didn't focus on them in advance and ask these questions, but there is the ultimate question of, is human genome material of various kinds different?

Bob has just pointed out what -- OTA recently, just in the last months, has published a report on ownership of human cells and tissues. That certainly is relevant to this and we all might pursue that.

DOCTOR COOK-DEEGAN: It's listed in your packets. One of the many documents in your packets is a list of OTA reports. There's another list of OTA reports under the auspices of another project, not this project but another project, called "New Developments in Biotechnology". The first volume in that was called, "The Ownership of Human Cells and Tissues". Some of the issues you're talking about were raised in that report, although none of them were resolved, of course.

CHAIRMAN LOWRANCE: Doctor Childress?

DOCTOR CHILDRESS: Addressing -- this question has been asked in a very important way, and I'm not sure how far this group will go in addressing it, but we are basically working by analogy with a number of existing statutes, court decisions, regulations and the like. You raised the question about whether there was something dramatically different about these that would force us, in effect, to some new conceptions.

Now how far we go in this today -- I'm a little curious about how you propose to limit the range of our discussion, because it does seem to me that this -- and even to point to the close connections between intellectual property and physical property concerns, this could open an exceedingly broad range of discussion.

How far are we going to be willing to go in this direction?

CHAIRMAN LOWRANCE: Not many limits to start with. More limits as the day goes on, let's say, as we watch the clock. I think OTA would be

best served by a broad discussion. The narrow parts we'll get to down the way.

Would you like to make an opening statement about that then?

DOCTOR CHILDRESS: Well, I think it's important to ask at each point what kinds of social or ethical values are served by any of the institutions we have in place, such as property, and what kinds of things would come up in this area that we would particularly want to promote or to avoid.

It seems to me that we will be looking at a number of issues including who provided funds, if we go be Susan's comment about the facts of the matter, but we'd also be particularly interested in whether there's something in this area that merits special social and legal intervention in order to promote human welfare.

We may well get into some conflicts about, you know, liberty versus welfare and so forth, but I think that would just be the general direction and I would point out that we shouldn't assume that the current physical or intellectual property conceptions

would necessarily be adequate for what we're doing. We may have to step back and ask what kinds of values would be served by the current ones or by modification.

CHAIRMAN LOWRANCE: Thank you.

Yes?

MR. GOULD: My company was involved in a litigation involving ownership of cell lines several years ago, and fortunately we were able to settle out, but I am aware that in California right now there is a litigation relating to the MO cell line which is currently trying to decide the exact same issue.

But I think if you look at the facts of the prior cases, they all go to taking of cell lines without knowledge of the intended use by the donor person. I would imagine now that we are all a little older and a little wiser that these same problems won't have to arise again, that there would be proper releases and appropriate legal documents which would track where the cells came from and so on.

So, I don't see this as being really a

problem for the future. It's essentially something that's behind us now, I would imagine.

CHAIRMAN LOWRANCE: Let me come around the table this way.

Mr. Karny?

MR. KARNY: Yes. I'd like to go back to the basic issue raised here about what is different about the human genome project with regard to ownership and communication. We're obviously operation under an assumption that probably something is different. That seems to be at least the working hypothesis.

I think it would be very useful to spend a good deal of time talking about that, obviously, and I'd also like to get Bob's initial views on that because clearly, it seems to me, that the assumption flies in the face of some policy decisions that have been made over the last several years with regard to communication and in innovation in ownership going back to 1980 with Public Law 96517 which permits retention of ownership rights by nonprofits and small businesses and federally funded research. And, going

back, you know, continuing through the 1986 Technology Innovation Act which also seeks to stimulate innovation through enhancement of private ownership rights, among a lot of other things.

So, in the face of that, I think it would be useful to begin to focus on what exactly is different here besides the obvious, well, it's the human genome and maybe it's a big project. Is that enough, or is there something more here?

CHAIRMAN LOWRANCE: Let's continue to come back to that. Let's give everybody a chance for sort of an opening shot here.

Susan, you had a response to Mr. Gould, I believe?

MS. ROSENFELD: Yes. I'm not quite sure that I agree that all of the problems relating to donating cell lines are behind us. I wish that were true.

I think the particular problem which comes up in that context is that very often the cell lines will be coming from somebody who is a patient in a medical institution, and although one can get so

called informed consent from a patient, the patient obviously is under a lot of pressure and is very anxious for treatment, particularly if they're suffering from something like cancer.

So, I think there's always a very real question in those circumstances, how informed is informed consent? Very often what the law tends to do in circumstances where it feels that you have parties in an unequal bargaining position, the law tends to intervene in those circumstances and really closely examines whether consent to something or waiver or anything comparable has really been given.

I think that the class of persons who may be contributing a lot of the materials which would be used in research comes from a class which really does not have, let's say, as strong a bargaining position as either the institution who would be taking the materials or a commercial company to whom the institution would give them for purposes of development.

So, I don't think that this is a closed book. I think that the courts may continue to look

at this area.

CHAIRMAN LOWRANCE: Okay.

Other opening comments?

DOCTOR CASKEY: I would just add a couple of additional points to this, George. I don't think it is solved.

I have not seen, on a human experimentation at Baylor, any declaration of release of the biological materials to a given entity, investigator, or stipulating the rules under which the investigator would operate. Having served on Genetic Study Section for NIH, we are well aware of numerous circumstances in which there was no particular statement of possession of a very valuable cell line which would be useful for investigation of disease entity in which the investigator would block the release of the materials only requiring someone else to go back to the original patient and collect it.

So, it has not been solved by explicit statement in most of the human experimentation committee releases.

MR. GOULD: Well, if it's not present, then

obviously the people have not learned the lesson. That's what I'm trying to say.

DOCTOR CASKEY: You've been involved --

MR. GOULD: We have learned our lesson, and I know that when we do obtain samples which are going to be earmarked for development of cell lines or biological materials which may have commercial end points, that we take extreme care to make sure that a proper release is provided, that proper compensation and consideration is given to the patient so that there is absolutely no question that they understand where the material is going, what purposes are going to be employed for development of this material.

I would think that that should hold up. Now, obviously, we cannot guarantee what a court might do in the future, but I would think that the legal issues that have been raised in the past can be obviated. Those issues really arose from absolutely no knowledge whatsoever by the patient. There was a complete taking without compensation or knowledge.

So, I would assume that we've learned at least to go beyond that point and I don't know in

this instance whether or not we're really talking about patient samples or we're talking about volunteered material which is going to be expressly used for this purpose. I would assume that you don't need to have materials derived from anything other than a normal volunteer for the purposes of genomic mapping, but I may be wrong.

CHAIRMAN LOWRANCE: Well, let me call on Bob to continue, if I may.

DOCTOR CASKEY: My only comment is that the lesson should have been learned, but I doubt that it has.

DOCTOR COOK-DEEGAN: I think Geoff raised an important point. One thing I'll point out is that this issue of informed consent and who owns human cells and tissues is really smack dab in the middle of this other report that we have just finished. So, I mean, I don't want to discourage discussion if it takes off from there, but I do want to get back to the point that Geoff made and maybe give a little bit of a historical introduction as to why I think this is a major issue in connection with mapping and

sequencing specifically.

Geoff did mention that there are intellectual property protections and the tendency in recent federal laws has been to try to liberalize the interpretation of what can be protected. Spurring economic growth, essentially, is the primary motivation.

One of the backgrounds for this workshop is the lack of clarity of what is special about human genetic information. In the scientific community, there has been a lot of discussion. At several of the meetings where I have attended, scientists have expressed a great deal of apprehension that much of the information would be kept in places where other people would have to replicate the work from ground zero to create the resource that generated the information and therefore would cost a lot more money than it would if you didn't do it. From the federal perspective, you'd be putting out money repeatedly to do the same work if this work is locked up.

The other is, is there something special about the fact that this is human genetic

information? Dr. Van Horn may -- you certainly know more about this than I do. I wonder if you might make a few comments about, where this affects specifically human genetic information, what might be relevant and what does make it special or not special.

MR. VAN HORN: In terms of patentability, recognize that the patent laws are very broad. Indeed, in terms of our interpretation, they seem to get broader with every passing year.

CHAIRMAN LOWRANCE: Oh, there is some question about that.

DOCTOR COOK-DEEGAN: Except in the Appropriations Committee.

MR. VAN HORN: So, our purpose is really to implement and interpret patent laws given the scope of judicial interpretations that we get.

In terms of products in nature or things that exist in nature, they have not been considered patentable for a long period of time, unless somehow they're changed, isolated, or you change a form. In that context, I would suspect that human genetic

information would not be different than other types of information that would exist in nature, be it a plant extract or what have you, in terms of whether or not it may constitute patentable subject matter, depending on the facts and circumstances of the particular case.

So, we would treat it in a much broader context in terms of the general scope of the patent laws that now exist, and look at it in that respect.

DOCTOR RUDDLE: Could I ask a question as a biologist? I'd like to get some response from the legal people here.

If an individual or a company simply sequences a segment of DNA, do they have some proprietary control over that? What are the legal ground rules?

MR. VAN HORN: Basically, if one takes something, whatever it is, that exists in nature and simply analyses it --

DOCTOR RUDDLE: Yes.

MR. VAN HORN: -- and provides, perhaps, some information about that that did not exist

before, if it doesn't change it in any way, generally the concept is that that would not constitute patentable subject matter.

CHAIRMAN LOWRANCE: Dr. Smith?

DOCTOR SMITH: I just wanted to raise the issue --

CHAIRMAN LOWRANCE: Would you speak up? We have some observers back pretty far.

DOCTOR CAHILL: Lousy acoustic room. It's difficult hearing.

DOCTOR SMITH: Well, I wonder if we should address the Freedom of Information Act. What's the thinking --

DOCTOR CAHILL: I can't even hear you from across the isle here, I'm sorry.

DOCTOR SMITH: What's the thinking on the Freedom of Information Act, in terms of access of getting into data banks if someone comes in with a request and says, "I want to see this"?

CHAIRMAN LOWRANCE: Any comments on the applicability of the Freedom of Information Act to this kind of material, this information?

MS. ROSENFELD: There's a lot of, I think, additional inquiries that would need to be made to answer your question.

The first would be, who owned that data base, because the Freedom of Information Act really applies to government agencies and not to private parties. In fact, there's even a decision in a totally unrelated context, holding that if an entity was performing work for the government, -- this was under the Medicare Act actually related to PSROs-- and was accumulating information in order to carry out the function it had agreed to perform for the government, that information was not subject to the Freedom of Information Act.

So, my threshold question to you would be, who owns that data base. Then the next question I would have for you is, how was information put into that data base? In other words, was there proprietary information put in and was it only given on the condition that it would be kept proprietary and kept secret?

There are provisions in the Freedom of

Information Act which are directed towards protecting proprietary information. There are also provisions in the regulations which address nonprofit institution's rights to develop inventions which have been made with federal funds, which deal with the government's ability to release information which it receives about those inventions.

I guess what I'm really saying, those are some of the factors that one would have to take a look at, but in terms of a strict yes or no answer about release, one would really have to look at the specific facts of the specific case much more closely.

CHAIRMAN LOWRANCE: Good question. Other comments? We're brainstorming at this point anyway.

DOCTOR WALTERS: I think past experience may be instructive in looking at a new issue like mapping and sequencing the human genome. When I try to think of a comparable development in biology in the past 15 years, I would think that perhaps the early years of recombinant DNA research might be one of the best analogies that we would have, in some

ways.

I think it might be instructive to look at the history of that development, the way host vector systems were developed, what was patented and what was not. Where did the serious problems arise as that new technique developed? I think we may find some areas where there were ambiguities and problems, where uncertainties did hold back the progress of research.

If we could learn from that and plan in advance to try to avoid the same kinds of pitfalls with gene mapping and sequencing effort, I think we would perform a great public service.

CHAIRMAN LOWRANCE: Is anyone aware of sticking points in this early development? That is, are things already coming up in the lab or in corporations or for funding agencies regarding proprietary aspects of information or material? Is this -- again, to get the discussion going --

DOCTOR CAHILL: Well, certainly. The identification of a gene locus in a common disease that's held for proprietary reasons is holding up the

broad science for the rest of the world trying to characterize that disease.

How long can an individual hold on to this information? Can he or she hold on to it at all from an ethical point of view? Of course, they have to repay the stock holders that invested to develop the locus of the gene. These are major problems.

CHAIRMAN LOWRANCE: And can you give the group a specific example of how that's happening right now?

DOCTOR CAHILL: I can't give you a specific example, because I don't know who's sitting on what right now. I mean, for example, I might take a very common -- pick any common disease. Schizophrenia. It's probably multi-locus, but there may be some very predominant loci. I'm sure that someone may have, in a given kindred, large family, a closely correlated RFLP or some other relationship with a gene, and be sitting on it. This will be a tremendous market. They may hold on to it for a given period of time until it's clearly shown that this is the locus, to get the advantage so other people can't get into the

same ball game.

So, that's obviously a -- and I just pulled that out of the air.

DOCTOR CHILDRESS: George, there may have been that situation with all the cluster of reports that came out on Alzheimer's. It was clear that not everyone discovered in the same week the same fact.

CHAIRMAN LOWRANCE: Dr. Alford?

DOCTOR ALFORD: Yes. I think one of the problems is, because I am part of an industry and we have an obligation to our investors, of course,-- but we also want to share in the scientific community.

So, how do we do that? How can we communicate and at the same time try to protect whatever proprietary rights we would have from a commercial view. That's very hard. We set up, you have to appreciate, personally I set over 60 collaborations with the scientific community on a one by one basis, and they're hard enough to do by themselves.

So, one would envision setting up a multi-

center collaboration, a multi-organizational collaboration, and it even gets trickier. We'd want to be a part of that, but how do we do that and still protect our investment for our investors who have invested for us to go on with this and we would like to be able to share that.

You know, when we, as George Cahill said, when we found, for instance, the linkage to cystic fibrosis, we didn't have any definitive test. What we'd like to do is to share that with others, communicate with those other people who are working also on cystic fibrosis. What is the best way to do that?

It is a problem. It is a problem today and it's just started, but we can see that's a problem as we go through 2,000, 3,000 geneticists. So, it's an interesting concept.

CHAIRMAN LOWRANCE: Yes.

Mr. Karny?

MR. KARNY: Yes. I think we ought to examine and challenge this hypothesis that industry is going to be sitting on information that others

might use solely to protect its proprietary interests.

From my view of the situation for the last many years, it seems like a lot of the holding of information relates first to valid reasons of compiling the data, writing papers, being sure your results are what you think they are. A more cynical way of putting that might be simply that researchers are, for their own scientific advancement, holding on to information until the appropriate time.

So, I think there are a lot of motives involved that may not necessarily be solely proprietary, plus, this issue had come up in the early days of recombinant DNA and so forth. I think the consensus became clear, and the consensus emerged that one of the whole goals of the patent system is to encourage people to disclose this information to the public with the recognition that they will protect their invention by a patent.

So, what generally has happened when these inventions are made in the laboratory, papers are written for publication, applications are written

from those papers, the applications are filed and the papers are published. So, the world does have the knowledge of that invention, and, I think, in a fairly quick way.

CHAIRMAN LOWRANCE: George Gould?

MR. GOULD: I'd just like to reecho that statement, because I think the history of the last six or eight years demonstrates very vividly that advances in the technology have been made available to the public rather quickly, probably more quickly than most patent attorneys would have liked for optimum protection.

Almost as soon as the patents have been filed, I think there've been scientific seminars given or public disclosures of key sequences. Things like receptors, which have been recently the attention of a lot of scientific investigation in the fields of IL-2, IL-1, and some other important biological molecules, have been described and immediately made available to the scientific community.

So, I don't see that kind of reticence and

holding onto material for, I would say, undue periods of time in order to fully capitalize on the technology. I think quite the opposite has happened. There has been rapid development, rapid exposition of these developments and the public has been able to move ahead in the technology.

DOCTOR CAHILL: We're talking apples and oranges, though. You're talking about patentable artifacts, etcetera. I'm talking about locus of a gene, which is not patentable in the first place, and therefore we're talking about something completely different. I completely agree that the patent process protects evolution advances.

When you're talking about loci of genes and also sequencing of genes, which is not patentable from what Mr. Van Horn just stated. It's important to sit on that information, because you can't patent it, as long as you can if you're looking only for a profit incentive.

MR. KARNY: It depends on what the invention is.

DOCTOR CAHILL: Its a different problem.

MR. KARNY: If the invention is a method of determining where a loci is, that is a patentable method. In the course of trying to secure that patent, there will probably be an example in there with your experimental results including that locus.

So, it really depends on the invention. As Charlie Van Horn said, the patent laws are very broad and information per se may not be patentable, but depending upon how you look at it, there is a lot of room for focusing on something that is patentable and protecting that, but at the same time turning the rest of that information over to the public.

CHAIRMAN LOWRANCE: Doctor Alford?

DOCTOR ALFORD: I guess, as George is suggesting, there's two types of disclosure of information. One is just disclosure, for instance, at a presentation at a scientific meeting or a journal article, then there's disclosure of the material itself.

Of course, being with a private industry, our scientific group is as quick to publish and to present as any other academic group. You have to

remember, it's not just the private industry that's holding -- for instance, if there's an idea, there's also problems with protecting rights in the academic community. The academic people also want to protect their information rights, but when there is a finding there is a rush to have that finding disclosed.

And so, for instance, we've written patents in two days so that our people can present. But once it is presented, unfortunately, as I spoke with Mr. Van Horn earlier, the patent process is quite a slow process. It could take several years sometimes to get patent protection, so one doesn't know if really that is the best way to protect one's rights. We're not convinced that trade secret has any value, unfortunately, in this area.

If we're going to have good communication and establish collaboration, it's going to be very hard to keep a lot of this information as a trade secret. How can we do them both? They seem to conflict with each other.

So, that's why there is a problem with disclosure, but the disclosure is informational

disclosure and it is also, don't forget, material disclosure.

CHAIRMAN LOWRANCE: Bob Cook-Deegan has a question for you.

DOCTOR COOK-DEEGAN: Just to clarify, perhaps, and crystalize the debate between -- I mean Geoff was taking about patentable stuff and George has mentioned stuff that really doesn't fit in the patent because it's raw data.

One of the grey areas is the whole process of determining a genetic locus, and I wonder if you could give us a little bit of the history and the status and show how the uncertainties about the RFLP process have been played out today and the relationship between integrative and collaborative and stuff like that.

Without putting you on the spot --

DOCTOR ALFORD: Thank you.

DOCTOR COOK-DEEGAN: With putting you on the spot.

DOCTOR ALFORD: I guess our best example is when we discovered a linkage to the CF locus. I

guess I have to go back to that.

When we discovered a linkage to the CF locus, we envisioned that that linkage was a linkage test. So, obviously, we filed for patent protection on a test of linkage. So when we had our discovery, our announcement was made three days later and we worked around the clock to file something at that time.

I think that's really what you're referring to, but it's with those other pieces of information that are hard to share. The information that we have put into the data bases, all of the 300 or 400 probes that we've developed, we'd like to be able to share those to get more information, to find out more, but I don't know how we can do that correctly.

Obviously we're not going to file, as you may be surprised. We're not going to file 500 patents on 500 probes and make 500 deposits. It may be that collaborative -- for instance, we'll file on diagnostic tests, we'll file on the identification of loci, we'll file on that kind of strain.

I don't know if that's the kind of idea

that you're looking for, but that's the strategy right now that we're taking. But that doesn't help us too greatly with sharing and with communication, because a lot of the information, probably 90 percent of the information that we're developing we do want to share and it's very hard to see how we can protect that information itself.

CHAIRMAN LOWRANCE: Very helpful.

DOCTOR CAHILL: I want to expand on that for the general audience here.

There are probably, in the open market, in other words the nonprofit sector, 300 to 400 RFLPs that are usable.

Am I correct Frank?

About that number. And these are probes to look for linkage with given diseases, for those of you who are not on top of what a RFLP is.

And the guess is that there may be another 500 or 600, just pure guess, in the commercial world, of which you have probably half, well over half.

DOCTOR ALFORD: Yes.

DOCTOR CAHILL: I mean, pure off the top--

we don't know how many you have, you just told us.

DOCTOR ALFORD: "About", I think I said.

DOCTOR CAHILL: "About". Well, we call it the "free world" and the "commercial world".

But with these large kindreds that the clinical people have, there's a parallel evolution. I'm looking at a disease between the "for profit" and the "not for profit". The cystic fibrosis is an excellent example, with two or three "not for profit" units and two or three "for profit" units all looking for the same probe, which could have probably gotten there much earlier with collaboration.

DOCTOR ALFORD: Yes, but don't forget, George, as I'm sure you are aware of, one tried very hard to strike up collaboration.

DOCTOR CAHILL: Yes.

DOCTOR ALFORD: And one tried for months and months with several collaborators around the world to establish something. Some of them were set up and are fruitful and we're very pleased with them, but some were not set up and some probably will never be set up unless there is a new forum, there's a

better way to protect both party's rights and to protect both parties feelings.

That's what we'd like to do and hopefully some discussion today will help us do that.

CHAIRMAN LOWRANCE: I think this afternoon we'll have a good chance to ask the Agency administrators what stipulations they are currently placing on various aspects of this puzzle or that they're contemplating putting on it or that they want guidance from the Congress on. That should be another cross cutting view this afternoon.

We haven't talked about instrumentation. Are instrumental methods and so on so analogous to existing inventions that there are no special questions regarding those? The fact that there's mixed funding in the development of some of those, NSF and the private sector, for example. Are there any complications there?

Mr. Van Horn, are you aware of any problems regarding protection, patentability, and so on, of instruments or techniques in this area that are unusual?

MR. VAN HORN: No.

CHAIRMAN LOWRANCE: Seems routine. How about bottles of material? I mean, that is chromosomal material or other things. We started out earlier, Mr. Stephenson raised the issue of the stuff itself, the very essence of chromosomes. What's the play on that right now?

Again, are there dimensions so far coming up that make that material different from pollen or blood samples or other cells? Can we see clear differences or problems where there's going to have to be policy resolution?

DOCTOR CAHILL: Can I ask, just to pinpoint it, is the chromosome specific libraries coming out of Los Alamos, which again is a federal agency, are those copyrighted?

In other words, if I'm running a small company and I use chromosome 16 specific library from Los Alamos and I find something on it, can I patent that in my own right? I'm using a publicly available, paid for by the government, collection of material.

I honestly don't know, and this is a -- in other words, I'm putting it up as a specific question of what you're asking.

CHAIRMAN LOWRANCE: Is there an answer around the table?

MR. GOULD: Well, there's experience in the interferon field where people have probed into various DNA genomic libraries and pulled out genes and then went ahead and identified them and engineered them into a useful form which became the key to a patent and you were able to patent that with no problem at all.

So, I don't see any problem with the --

DOCTOR CAHILL: But you are using the raw material to do that, to derive your patent.

MR. GOULD: Yes, but one is an intellectual property right and the other one your worried about, if you properly received the material and there's no restriction on your ability to get a patent and I don't think there would be, you should be able to do it.

CHAIRMAN LOWRANCE: Susan Rosenfeld, did

you have a comment?

MS. ROSENFELD: Just a brief one. You made reference to copyright with respect to sequencing. Is that right?

That suggestion has sort of been -- the suggestion that one can copyright recombinant material or genetically engineered organisms, however you want to describe it, has sort of been floated around. I do not believe it has really received widespread acceptance, but it is a suggestion which has been made. In fact, it was a suggestion which Bob asked me to comment very briefly on in my remarks.

Basically, the concept behind it which has been articulated, among others, by Professor Kayton, is that DNA is like computer programs and since computer programs can be copyrighted, DNA can be copyrighted. That's his view. This is not necessarily a view which is shared, as I said, very widely.

MR. VAN HORN: If at all.

MS. ROSENFELD: No, actually, I think it is

shared by at least one other --

MR. GOULD: Mr. Kylee.

CHAIRMAN LOWRANCE: Let me, at this point, just so we can stay with out agenda, we'll come around and around these questions all day and it's getting exciting, let me ask Bob to give background to OTAs discussions with the Bar Association and then introduce Susan's -- ask Susan to give her proposal.

DOCTOR COOK-DEEGAN: Before our last panel meeting, I guess probably starting in January and February, if fact, Susan had written to me at OTA. Somehow the network has been working pretty well. People have been finding out that there is an OTA project on the human genome going around, and Susan had written me on behalf of the Science and Law Committee of the Association of the Bar of the City of New York, which is a very long title which I've since memorized, asking if there is any way that they could be of assistance.

When she first wrote, I didn't know what they did and they didn't know what we were doing. So we exchanged some information, and then between the

time that we first talked and the time that I called her back we had our panel meeting and another historical event took place. Walter Gilbert, who was on the NRC panel and has been quite active in participating in the debate about whether there should be or should not be a major federal effort to sequence and/or map the human genome, pulled out of the NRC panel and chose to start his own company up in Boston.

A few of the reports in Business Week and in the New York Times and a few other places stated that he intended to copyright the data that he would produce and it became clear between the panel meeting discussion that we held on April 6th and reading the business press, that we needed to find out more about what was going on.

That's one of the fundamental bases for this workshop and it also gave me at least a starting point for the discussions with the Association of the Bar. After about five minutes, we exhausted my knowledge of intellectual property and we have just done so again here.

So --

CHAIRMAN LOWRANCE: Susan, would you make your presentation?

MS. ROSENFELD: Sure.

CHAIRMAN LOWRANCE: You have given us a copy of your statement?

MS. ROSENFELD: I believe everybody has a copy of my statement. I also believe everybody has received a copy of the letter, which was sent out by the president of the Association of the Bar, sort of outlining some of the issues which I'll talk about at a little greater length this morning.

Before I start, let me just give you a little background as to how and why the Association is involved in this issue at all, because it may not be immediately clear to everybody. The Association has a Science and Law Committee and independently of OTAs efforts, the Science and Law committee several months ago decided to take a look at some of the legal and social issues which would relate to a gene mapping project, not necessarily in terms of a collaborative project, but just in terms of the

actual mapping of the human genome itself.

As a result of that, we started looking around to see who else was exploring some of these issues and that's how and why I made contact with Bob and you know the rest.

The Association of the Bar itself very frequently gets involved in issues which go beyond just the strict legal analysis and has a long history of involvement in social aspects and legal aspects of public policy issues on a local, state, national, and even international level.

Now let me proceed to my statement. What I thought would make the most sense would be for me just to go through it with you and at the end if you have any questions, feel free. The purpose of the statement is to try and identify some of the issues which you might like the Association to pursue in more detail in its report. So, let me begin.

I've been asked to briefly describe some of the ways intellectual property laws might limit the use and exchange of information, processes, and materials during a federally sponsored human gene-

mapping collaboration. This morning I will elaborate upon some of the issues summarized in the letter from Robert Kaufman, the President of the Association. My presentation will be somewhat general, because I do not know how the gene mapping project will be structured or the number and types of organizations that will participate.

I will assume that during the course of any collaboration, certain materials and methods will be developed which will qualify for protection under the intellectual property laws. I will not attempt to identify particular items that fall within this category. In addition, because of time, my remarks will concentrate on issues relating to collaborative efforts occurring solely within the United States.

At present, there are substantial collaborations between universities and industry in the field of biomedical research. While the size and complexity of these collaborations do not appear to equal that contemplated by the gene mapping project, they nonetheless would appear to present, albeit on a smaller scale, many of the same types of problems.

An examination of the strengths and weaknesses of existing collaborations, therefore, might provide guidance in the planning of this project.

With this introduction, let me now proceed to a discussion of some specific issues. My remarks will be divided into two parts: the first will address some potential problems which might arise as a result of the intellectual property laws; the second will address certain possible solutions.

To begin, I would like to describe some of the ways in which intellectual property rights could limit the use and exchange of information, processes, and materials among investigators.

First, patents. Generally, anyone who makes, uses or sells anything subject to a patent without the consent of the patent owner will be guilty of infringement. This would be true regardless of whether the unauthorized production, use or sale was committed by a person working in industry, a university or government, and regardless of whether the patent holder was a university, industry or government.

This prohibition would apply even if the unauthorized conduct were by someone who had independently developed the invention after the patent holder or by someone who was unaware of the existence of the patent.

Patent infringement can be avoided by securing the consent of the patent owner. In addition, the federal laws governing inventions made with federal funds, which I will discuss later, may provide a means of avoiding infringement in situations in which the owner has not given consent.

However, there is an exception to this blanket prohibition which I would like to mention now - the so-called "experimental use" exception. This is an exception which is not explicitly contained in the patent statute, but has been recognized in judicial interpretations. The exact parameters of this exception are not clearly defined although the decisions do indicate that "experimental use" in furtherance of commercial purposes may not be exempt. From OTA staff papers on the gene mapping project, it appears that one of the possible goals of a gene

mapping collaboration would be technology development, which I assume could entail certain commercially-related activities. The extent to which the "experimental use" exception could be relied upon in these circumstances would require a review of the particular facts involved.

Now let me briefly touch on copyrights and some of the limitations they impose on third party use.

If particular project results are covered by copyright, the copyright owner has the exclusive rights, among others, to copy, display and distribute copies of the copyrighted work for the term of the copyright. In contrast to the protection afforded by a patent, a copyright does not give the owner the right to prevent someone else who has subsequently and independently created the identical work from using or even copyrighting it.

There are two exceptions to copyright protection which could be of particular significance to a gene mapping project. First, copyright protection is not available for any work of the

United States government. This is defined under the copyright law as "a work prepared by an officer or employee of the United States Government as part of that person's official duties." 17 U.S.C. Section 101. Work falling within this definition, therefore, would be within the public domain and not subject to the restrictions to which I have referred. However, this exemption, by itself, would not appear to prohibit the creation of copyright in works prepared under a government contract or grant.

Another exception to a copyright owner's exclusive rights is the so-called "fair use" exception which can be thought of as somewhat analogous to the "experimental use" exception under patent law. Like the experimental use exception, the determination of whether a particular act will qualify as "fair use" must be made on a case by case basis.

The next issue I want to discuss is the manner in which a university's or scientist's desire to secure intellectual property protection for the products of research could limit publication and

other research disclosures. The intellectual property laws require that certain conditions be met in order for inventions to be protected. For example, under the United States patent laws, a United States or foreign publication describing the invention more than one year prior to the filing of a patent application will bar a patent. Under many foreign patent laws, publication before the filing of a patent application is an absolute bar to a patent. Out of a desire to avoid the application of such laws as this and insure that proprietary rights are protected, individuals and institutions may be reluctant to share information and materials.

Information exchange also could be limited because a university currently doing mapping research may already have an agreement with a commercial company for the development of the results of this research. Included in the agreement could be provisions prohibiting or otherwise limiting the university's right to share results with other groups.

Another issue to consider is potential

conflicts over ownership of intellectual property rights in the products of mapping research. A desire to avoid having to share title to research results could discourage individuals, universities and private companies from giving other project participants access to information and materials which they have developed. In addition, disagreements or confusion over ownership of research products subject to proprietary rights (for example, because of commitments arising from multiple funding sources) could make it difficult for a project participant to obtain the necessary consents to use such results.

A federally sponsored gene mapping project presumably would involve the expenditure of large amounts of federal funds. Therefore, it is important to consider the impact of the federal laws promoting the development and marketing of inventions made with federal funds. This would include, for example, the legislation on "Patent Rights in Inventions Made with Federal Assistance", 35 U.S.C. Subsection 200 et seq., and the "Federal Technology Transfer Act of

1986", Pub. L. No. 99-502, 100 Stat. 1785 (codified at 15 U.S.C. Subsection 3700 et seq.).

In 1980, Congress enacted legislation, which subsequently has been amended, to govern certain matters relating to patent rights in inventions made with federal assistance. The purposes of this legislation include promoting "the utilization of inventions arising from federally supported research and development" in conjunction with "encouraging collaboration[s] between commercial concerns and nonprofit organizations [such as] ... universities." 35 U.S.C. Section 200.

Generally, the legislation gives nonprofit organizations the right to elect to take title to and license patentable inventions made with federal funds. The legislation requires a contractor which elects title to file a U.S. patent application on the invention. The contractor may also file foreign patent applications.

The Federal Technology Transfer Act of 1986 was adopted for the purpose of improving "the transfer of commercially useful technologies from the

Federal laboratories and into the private sector." S. Rep. No. 283, 99th Cong., 2d Sess. 1, reprinted in 1986 U.S. Code Cong. & Admin. News 3442. The Act authorizes each federal agency to permit the director of any of its government-operated federal laboratories to enter into cooperative research and development agreements with other government agencies, industry and nonprofit organizations, and to license government owned inventions.

In addition, the Act provides that if a federal agency does not intend to file a patent application or otherwise promote commercialization of an invention, the agency must allow the government employee who was the inventor to take title. Under these circumstances, the employee can seek to secure intellectual property protection for the invention.

Thus, both of these statutes promote intellectual property protection and, to the extent such protection may be inconsistent with communication of research results in a gene mapping project, could limit such communication as well.

Now I would like to briefly discuss some

possible ways of minimizing limitations on the use and exchange of research results in a gene mapping collaboration.

Let me begin with the federal legislation governing patent rights in federally funded inventions which I have just been discussing. This statute contains several provisions which might form a basis for promoting exchange of research results. Because of time, I will only list these provisions. In order to determine their impact, a much more detailed analysis would be required.

(1) The statute provides that if a contractor elects title to a federally funded invention, the federal government "shall have a nonexclusive, nontransferable, irrevocable, paid-up license to practice [the invention] or have [the invention] practiced for or on behalf of the United States" throughout the world. 35 U.S.C. Section 202(c)(4). The extent to which the federal government could rely upon this license as a means of dissemination research results is an issue which could be explored further.

(2) The statute also provides that the funding agreement may provide the United States with additional rights "including the right to assign or have assigned foreign patent rights in the subject invention," as the funding agency determines are "necessary for meeting the obligations of the United States under any treaty, international agreement, arrangement of cooperation, memorandum of understanding, or similar arrangement." Id. This provision might be relevant to the international collaborative aspects of the gene mapping project.

(3) The statute provides that a nonprofit organization may elect title to a federally funded invention except "in exceptional circumstances when it is determined by the [funding] agency that restriction or elimination of the right to retain title to ... [the] invention will better promote the policy and objectives of" the statute. Id. Section 202(a)(ii). If the agency makes such a determination, it may be appealed by the affected contractor. An issue to consider would be whether federal retention of title to certain gene mapping

research results could satisfy the requirements of this provision.

(4) The statute permits a federal funding agency to require a contractor to license an invention not made under a federal funding agreement to third parties if the head of the agency determines that the use of the invention is "necessary for the practice" of an invention covered by a funding agreement or "for the use of a work object of the funding agreement and that such action is necessary to achieve the practical application" of the funded invention or work object. Id. Section 202(f)(2). This provision might serve as a basis for providing access to techniques and materials developed by a project participant without federal funds.

(5) The statute authorizes the federal government to grant, or cause a federally funded nonprofit contractor electing title to an invention, or its exclusive licensee, to grant, third party licenses with respect to the invention (so-called "march-in" rights). A federal contractor or its exclusive licensee has the right to appeal the

exercise of "march-in" rights.

"March-in" rights can only be exercised in certain circumstances, which would include, among others, the following:

(a) action is necessary to alleviate health or safety needs; or

(b) action is necessary to meet requirements for public use specified by federal regulations.

An issue to be explored would be what types of situations would satisfy these statutory standards so as to justify the exercise of "march-in" rights.

In addition to relying on these statutory provisions, consideration could be given to incorporating into funding agreements with project participants the obligation to share research results. An evaluation of this approach should consider the extent to which the federal government would be authorized to impose this requirement on a contractor in light of the federal legislation promoting the development of proprietary rights in federally funded inventions.

Finally, as I indicated earlier, one way to address limits to dissemination of research results would be to obtain the permission of the owner of a patent, copyright or trade secret to access and use. This approach would be similar to what has been done in other multi-institutional collaborations.

For example, information and materials might be shared for research purposes under confidentiality and restrictive use agreements. Licenses for certain techniques and materials might be obtained by participants in the collaboration. Collaborative research agreements could define the relative proprietary rights of research participants. Licensee agreements could be developed defining the basis upon which information for and access to databases would be provided. Collaborators could agree to uniform policies on publication. While such contractual arrangements might not solve all of the problems, they certainly could be useful.

I will only briefly mention trade secrets and other confidential information, which are governed by state rather than federal law. At

present, these would not appear to be of the same importance to a university as patents, because of the importance of publication and free discussion in the academic community. Unlike patents, the existence of a trade secret will not prevent someone other than the owner of the trade secret from independently discovering and using the subject matter of the trade secret.

Finally, there was a suggestion in the agenda materials that trademarks might pose a problem with respect to exchange of data and materials in a gene mapping project. Since a trademark is merely a means of identifying the source of goods, it would not appear to be of significance in this context.

I hope my remarks have been helpful in giving you an idea of the range of intellectual property law issues which might arise during a gene mapping project. I also hope that it will enable you to identify the issues you would like the Association to focus on in its report.

Thank you.

CHAIRMAN LOWRANCE: Let's take just a brief

minute to start our discussion, take a break and then come back and continue discussing Susan's proposal.

First of all, I would ask whether topics occurred to you as she talked that weren't covered. Was there anything that she didn't bring up that you thought should be in the hopper?

MS. ROSENFELD: I can't believe that there are no other topics.

CHAIRMAN LOWRANCE: Sort of thing you can knock off in a week or two.

Comment here.

MR. KARNY: I think the paper is a good start and had a lot of the important issues.

Perhaps one additional topic is the broader one or the tougher one of the general policy underlying the Technology Innovation Act and really how this issue fits in in terms of whether protecting intellectual property rights is going to actually hinder the dissemination of information or help it.

Now that's going to be a tough and amorphous issue and perhaps it's inappropriate here. One the other hand, we may be focusing on some of the

rough parts of that, but in the broader perspective the protection of intellectual property rights arguably -- at least the policy underlying the Act takes the position that the protection of those rights will ultimately allow the greatest degree of dissemination of information.

CHAIRMAN LOWRANCE: Other comments?

Doctor Walters?

DOCTOR WALTERS: I simply have a factual question about the relative importance of trade secrets and patents in commercial biotechnology currently. I don't have a way to get at that information and if trade secrets are equally important or perhaps more important than patents, then I think that means that just developing an excellent patent policy is not going to be sufficient.

DOCTOR ALFORD: Right. If I could help, that's what I was trying to address before with my remarks, to be honest with you. That's why I don't see -- one cannot keep a trade secret if we're going to do this kind of project.

I don't think there's any value just to keep things as a trade secret, but in order for me to share my information with you there has to be some kind of a collaboration, some kind of arrangement, something set up so that I can share that information freely with you and you can share your information with me.

But I have to have some way to protect my secret if I will develope into something that has commercial benefit, because I have an obligation as being a commercial company to my investors to do that.

So, I guess it's very hard. With the patent it's easier, when you look at it, except of course, the patent process is a very slow process. But in the meantime, I don't want to wait for a patent in order to be able to be able to speak with you and to communicate with you. I want to speak with you when I have the finding.

So there has to be some way to establish a collaboration, some kind of arrangement so that I can share information and you can share information with

me at the same time.

CHAIRMAN LOWRANCE: Other points?

Yes, Mr. Van Horn?

MR. VAN HORN: Also, I think, a point is that you are dealing not only with a national law, but, as you mentioned, you're really dealing with an international marketplace. You can often conceive laws in the United States that will facilitate, such as the grace period in patents, facilitate communication without really losing your right to a patent. The same act, in trying to establish a right in a foreign country like Japan or Europe, that's going to be an absolute bar to getting that kind of protection.

So people will act in a way that will minimize the risk of losing rights, whether it be in the United States or in the international marketplace.

CHAIRMAN LOWRANCE: Doctor Cozzens?

DOCTOR COZZENS: I just wanted to point out, and I'm sure we'll discuss this more when we get into the full discussion, that time is a word -- how

long it takes to get the access doesn't enter your discussion at this point, but it needs to in the end.

Since most of the mechanisms that you've outlined for opening up access would take a very long time to play out, and the essence of the problem seems to be getting information to people as quickly as possible so that research can move forward, I think that probably needs to play a larger role than it does at present.

MS. ROSENFELD: I certainly agree with what you're saying. I think that one of the things I was contemplating with respect to the mechanisms which I mentioned, would be in the sense of setting them in place initially at the beginning of a collaboration so that they would then, in a sense, run through the course of the whole collaboration.

For example, if someone enters the collaboration and they sign whatever agreements for exchange of information up front, just as one example, then those agreements would apply to everything which was developed by that particular participant throughout the course of the

collaboration. So while there might be some initial delay in the initial phase, once you sort of got going, you'd be over that hurdle.

Now I recognize that some of the suggestions relate to regulatory provisions and require Agency action, which presumably could take a longer period of time than just a contractual arrangement. But again, one might consider the same kind of philosophy, which is to do what had to be done up front and then you're all set for the duration. But that's certainly an issue which needs to be considered.

CHAIRMAN LOWRANCE: Doctor Caskey?

DOCTOR CASKEY: Susan, have there been examples in which information was so valuable that it was decided that it should not be protected, that there should be free and very open exchange of information?

Wouldn't that eliminate many of the legal considerations, that this was a no no area?

MS. ROSENFELD: When you say "decided", do you mean decided legislatively?

DOCTOR CASKEY: That's right, that you eliminate the subject.

MS. ROSENFELD: There may very well be. I cannot really answer that at this point, but I think it's safe to say that there is a great deal of information which is considered proprietary even though it may relate to such subjects as human health and welfare, which I guess is --

DOCTOR CASKEY: I'm just saying that the knowledge of man, the collective organization of man is of such high value that it would supercede any legal authoritative boundaries.

MS. ROSENFELD: You mean as a general constitutional principle? I think that is not an argument which is certainly widely made and accepted.

DOCTOR CASKEY: But this is the first time we will gather such information.

MS. ROSENFELD: Let me put it this way, I think that that is something which could certainly be explored, but in terms of, at this point, absent of any further statutory or regulatory action, I think that there could be problems in resting on that

concept as a means of having research results disseminated.

DOCTOR CASKEY: I want to come back to it. I know we're going to have a break, but figured we wanted to make the outlandish statements first and then come back --

CHAIRMAN LOWRANCE: That's a very good comment.

MS. ROSENFELD: Just on little addendum. In the references that I made to the legislation governing federal inventions, there are provisions in that which focus on health and safety needs. But, again, that's not across the board. That requires a specific agency examination of the facts and issues and a specific determination that the particular substance or materials at issue meet the criteria of health and safety needs. If that's the case, certain consequences will flow from that which would presumably result in broader dissemination of research.

But that kind of a concept would really require more than just somebody outside of government

saying, yes, we believe that something is health and safety and shouldn't be subject to intellectual property protection.

CHAIRMAN LOWRANCE: I just would recall a historic example from my own institution back in the very old days of the '20s, when Professor Donald Van Slyke invented the blood pressure cuff. There was a big discussion within the then Rockefeller Institute for Medical Research over whether to patent this incredible discovery, because it would revolutionize our basic understandings of physiology and was clinically applicable and all the rest.

The was a big discussion. The Universities Board of Trustees decided, indeed, to take out a patent on the discovery and then give it to the world and that's what they did.

Now with that, if I may, could we break? This will continue. Remember your comments. Let's pick up right where we are.

DOCTOR WALTERS: Those were the days.

CHAIRMAN LOWRANCE: It was before even my time.

The rest-rooms are about 100 feet down that way and there's coffee here. We'll reconvene in ten minutes.

(Whereupon, at 11:07 a.m., a recess until 11:21 a.m.)

CHAIRMAN LOWRANCE: Well, we've gotten ourselves to an interesting point and we've certainly put a number of important issues on the table. Let's just pick up the discussion right where we were. We have now until 12:15, so not quite an hour to bring this to maturity.

There were several comments just waiting to be expressed as we broke to go break.

Mr. Karny, did you have a comment?

MR. KARNY: Yes, I guess, just to follow up on a couple points with regard to whether anything is excluded from patentability now. As Susan said, it's really handled in the context of a compulsory licensing type situation and the "march-in" rights in the 96517 is a perfect example.

There are also compulsory licensing provisions in the Pipeline Protection Act, a little

far afield, I recognize, from this, but again the idea was there was something special about agriculture and plants and food plants that, in certain situations, if somebody had property rights and there was an idea that they weren't meeting some really significant demand for food or whatnot, that the owner could be forced to license them to people.

I guess compulsory license rights are something of an anathema to patent attorneys, but it may be something that could be considered, in the context of this, as special.

CHAIRMAN LOWRANCE: Other comments? Yes, Mr. Gould?

MR. GOULD: I believe that legislative prohibitions against patenting of methods of treatment for human disease in pharmaceutical products have been tried in a number of countries and I think, to all extent and purposes, have failed miserably in the intent. Most of those countries like Italy, Canada and so on have essentially dried up as places where one carries out research. I think the net effect has been to swing the pendulum the

other way and the encourage extension of patent laws rather than inhibiting their strength.

CHAIRMAN LOWRANCE: Doctor Stephenson?

DOCTOR STEPHENSON: I think this is a real public policy issue because although the purist might say, "Well, there shouldn't be any patents or there should be no proprietary rights in any of this type of information," unless there is some proprietary right or whatever, the desirability of people investing money in the research certainly goes away.

The instance that you cited with regard to the sphygomonometer, I think in cases like that, the patent is for the protection of the ability to have the right to give it away. That's a very important issue because if you didn't do that, then anybody could go in and patent it and preempt your rights.

So, I think the patent law, if anything, should be strengthened. Certainly, as a matter of international policy, I think the Congress could very well consider legislation to make sure that people do join the Paris convention and do, in fact, provide a worldwide climate where these rights are recognized,

respected and protected. That would probably be the best way to insure the rapid development of research and facts in this area.

CHAIRMAN LOWRANCE: Let me ask Susan Rosenfeld, do you have any questions for the group as we move back to a broader discussion? You're going to be with us all day and therefore can take notes. I'd urge us, at any point, if we have afterthoughts for Susan, that we simply bring them up.

MS. ROSENFELD: What I think would be helpful to me is to know from the laundry list of issues which I raised which ones the group feels are of most relevance or concern to them.

CHAIRMAN LOWRANCE: Does anyone have any votes on that at this point? We may want to come back to that later in the day, once we've had our full discussion. But is there any one single issue that people around the table would like to endorse as being high on her list?

Okay. You may have thoughts about that later.

Mr. Karny has a comment.

MR. KARNY: I like what Susan has done with the various parts of the acts regarding exemptions from a normal situation where somebody retains ownership. You've gone into perhaps how some of these areas could be explored and how licensing arrangements could be used creatively.

For example, in the context of a federal center that might be doing this type of work, how people involved could have agreements with regard to the sharing of the work, using basic concepts and licensing law within the context of the policies enumerated in existing statutes. I think there may be a fair amount of flexibility there to reach the goals of fast sharing of information, yet protecting some various types of property rights and also giving particularly private companies incentives to be involved in these situations.

CHAIRMAN LOWRANCE: LeRoy Walters, did you have a comment?

DOCTOR WALTERS: Yes. It's not directly responsive to the question about priorities in this document.

I've been trying to think of analogies to the enterprise of mapping the human genome. I wonder whether the international epidemic of AIDS and the attempt to develop vaccines or chemotherapies might be worth thinking about as a parallel current development.

There we have a public health emergency and it would be very interesting to know what policies are being developed in that case as far as proprietary rights are concerned, as far as any mandatory sharing of information is concerned where federal money is involved and where federal money is not involved.

In this case, we don't have a public health emergency in the same sense of an infectious disease. On the other hand, we do have an international plague of genetic diseases. This project may lead toward--certainly will lead toward better diagnosis and perhaps in the long run toward cures. I don't think we should lose sight of the potential long-term benefits for human health and animal health as well from this project.

So, I would be interested, if anyone has information about what's happening on the AIDS front currently and whether any exceptional causes are being called upon to try to deal with that epidemic.

CHAIRMAN LOWRANCE: Any responses to LeRoy's question?

DOCTOR CAHILL: I have essentially the same. You took it right out of my mouth, but I was a little more explicit. I had a long night last night. We put together a six amino acid peptide that blocked the entry of the AIDS virus into the T-4 lymphocyte. I want to go to Mr. Karny to patent it and then I'd like to take the next three or four years to start up my own little private company so I can market this product.

MR. KARNY: So?

DOCTOR CAHILL: So, can I sit on it for three or four years and develop my own company to do this?

MR. KARNY: No need to. Once you file the application, you can tell anybody you want about this.

DOCTOR CAHILL: But I want to keep it to myself. I don't want to let it out. I'd like to keep[the family, my brother working with it, my Uncle Bill to be the secretary of it.

MR. KARNY: It's your privileged.

DOCTOR CAHILL: It's my legal privilege. That's the point.

MR. KARNY: Well, the issue is whether ethics override recognized property rights. Clearly, you've got a property right in this thing. Let's get away from the "legalistic" aspects of this and look at it from a very basic perspective. But for your actions, this thing would not exist. So let's keep that in mind. It's not like you're taking something from the world that it should have. Your efforts, activity, hard work, creativity, money, whatnot led to this. So you have something.

Our society recognizes your right of dominion of that. It encourages you to turn that over to people in various ways, such as through the patent system, but you don't have to. So, unless we're going to change some basic constitutional

rights of private property, then we need to ask the question, do ethical considerations override these property rights and to what extent and how can we deal with that? If the federal government is funding the creation of this property, can they put stipulations, obviously, on who has rights to that property?

At some point, we really need to, and obviously will, address those overriding ethical questions.

CHAIRMAN LOWRANCE: George Gould?

MR. GOULD: I'd just like to point out on the other issue as to whether there are preexisting arrangements that might serve as models. I'm aware of a multicenter research program in malaria, a malaria vaccine, which I don't know whether you've looked at. You might want to consider looking at those documents that govern the exchange of information and proprietary rights in that field.

DOCTOR SMITH: Just on the point of models, in physical sciences what usually happens with a large-scale project between the United States and

Europe is that there is a memorandum of agreement drawn up and the data is available to a researcher for a year after which time anybody can have access to that data. So, the time period that was referred to by Susan, usually in physical sciences is a year.

The memorandum of agreement, as far as I know, that only covered very centralized facilities, accelerators, scientific spacecraft and usually the amount of time that's divided between the Europeans and the U.S. goes very much along the lines of how much money has actually been put in. So, if the U.S. puts in 75 percent of the development costs of the technology, they get 75 percent of the observing time.

CHAIRMAN LOWRANCE: Other comments?

Yes, Doctor Childress.

DOCTOR CHILDRESS: It seems to me that in addition to kinds of specific points that have been raised there has emerged in several comments a question of perspective that probably ought to be kept in mind. I don't know whether the perspective has already been shaped in such a way that it would

be inappropriate to do so, but this is set up in terms primarily of the way in which current laws would limit.

I heard Mr. Karny and Bob Stephenson and others comment that there would be a fundamental shift in perspective if you asked not only how do the laws limit, but how might it facilitate. Now, is that the kind of broadening that seems to be appropriate? It would then force you, I think, to get back into the broader questions of the values that would support or be supported by or be realized by one approach rather than the other. That's one point.

A second point, you're quite right to suggest that a big question is when would ethical considerations, if ever, override existing or recognized property rights? However, I think it is also important to keep in mind that there are already recognized ethical exceptions, some of which have been built into mandatory licensing. But the property doesn't exist in a kind of vacuum.

There are all kinds of constraints in terms

of abuse, destruction, transfer, et cetera, et cetera. It seems to me the fundamental question we're raising is whether, in terms of this bundle of rights we talk about under property rights, there are some that are more appropriate or less appropriate, defensible or less defensible in this particular area.

So, the question is, which kinds of ethical considerations, if any, ought to be limiting?

CHAIRMAN LOWRANCE: What's an example? Keep going.

DOCTOR CHILDRESS: Well, examples that quickly come to mind in other areas, there have been recognized quasi-property rights in the body and its parts, for example, meaning that they couldn't be transferred for commercial purposes, but they could be transferred. Well, there are all kinds of policy limits that are built in. And it seems to me the debate is when we should or should not be building some of those into a particular area.

Property is not just a given, it is a social construct. What kinds of rights under the

heading of property should be recognized in what areas?

CHAIRMAN LOWRANCE: I'll seize the fact that there are no hands in the air to ask Doctor Cahill, it seems to me that you're suggesting that there ought to be freer exchange and that you're troubled by the fact that there are people like your earlier self who had this discovery and is going to sit on it.

I wonder if you'd say a little bit more. I'm reading between the lines since you're trying to tell us that there --

DOCTOR CAHILL: Well, we've had this interesting change. For 50 years, a lady has a baby and the placenta is then used for all sorts of purposes, development of proteins, without her permission and no one's ever questioned this. She should theoretically -- it's part of her. She should theoretically have some interest in that part of its been done for commercial purposes.

Now, it hasn't been big bucks, but genetics is big bucks, as is AIDS and other things. So now,

the legal side is beginning to think about these things in much greater terms as commerce has moved in.

Or, to be more ludicrous, if the placenta isn't used, it's ground up in a triturator and flushed down and then it's eventually sold in some towns for fertilizer out of the town's septic system. I'm being ludicrous here. She should still have a commercial right because part of her went to help the town and its own town budget. That's being facetious in a way, but I'm just going that far. No one's ever questioned that.

But now we're questioned if someone takes a little bit of tissue and it turns out to have tremendous commercial value. Then all of a sudden everyone rears up and says, "My God, this is part of me." So, I'm asking for a kind of consistency in all of this. When there are big bucks, then we begin focusing down and when the ethics override the bucks, we don't come into it. But when the ethics to bucks ratio overrides, then I think the legal side has to be suppressed.

That's essentially saying what Roy was working his way up to. That's what we're going to find with the human genome. It's bigger, in many respects, and it's potential is immense. To have little packets being hidden away for profit and duplication, I think we really have to consider this in a broad stroke.

CHAIRMAN LOWRANCE: Yes, Doctor Stephenson?

DOCTOR STEPHENSON: I think the philosophical issues are difficult and many people have not wanted to address them at that level of discourse. I know for a fact that the Mitsubishi Corporation has as one of its stated corporate goals the mapping of the rice genome and the owning of rice. Now, that, to me, is a frightening thing, that anything like that could be legally construed to be the property of any one company or individual or whatever.

Leon Kas brought up some of these issues when we dedicated the new wing of our building, about should anyone have the ability to own something like that, own mule, own dog, own cat or whatever. I

don't think so. I think that there is a finite limit to which man should exercise his hubris.

But those are the issues that are never addressed in the public arena. We address minor issues comparatively. We make laws about them and so forth and it's sort of like an accretion that we arrive at a policy position by making lots of little bricks rather than look at the total plan of the edifice.

I think it's necessary in meetings like th is to at least bring up some of these larger, more global issues and discuss them, if only to say we don't have the means to deal with them. But they should be out there and exposed for everyone to see.

What you're saying, in essence, and what the whole purpose of this meeting is about is should anyone really have the ability to own the human genome as a proprietary piece of information. I bring up the issue of whose genome is it that we're going to own? Is it going to be generically man as mankind, meaning an average of all the people on the earth, or is it going to be 30 year old caucasian

male or is it going to be a 32 year old negro female? I don't know.

But that is a question which needs to be addressed if you're going to talk about mapping the genome. Whose genome, what kind of genome and what are the properties of it?

CHAIRMAN LOWRANCE: First, a comment on that, Doctor Ruddle?

DOCTOR RUDDLE: Well, you alluded to this earlier, Bob. I think most people are thinking now that the sequencing of the genome or the analysis of the genome is going to not be focused on one specimen. It's going to be a number of different sources of material and that doesn't pose any limitations on the analysis because we're all genetic mosaics anyway.

I think what's important is that the source material be well characterized and it be preserved and accessible so that one can recheck the information that's been isolated and been gathered.

So, I think the question of whether there's a type specimen or not is probably irrelevant to

these discussions.

DOCTOR STEPHENSON: I would disagree with you on that because if you were going to patent something, the type specimen becomes highly relevant to the --

DOCTOR RUDDLE: Well, it won't come from one person, let me put it that way.

DOCTOR STEPHENSON: But then is it possible to patent it?

MR. GOULD: Sure.

DOCTOR RUDDLE: I have no idea. But I would like to expand on what you were saying before and just ask again, I think I already asked the question whether just simply reading the sequence gives one the capacity to get patent protection on it. I think it's been answered quite clearly, that there is no grounds for patenting.

How does this relate to copyright protection? Is it possible by reading a sequence to obtain some kind of copyright protection on it? From what I gathered before you began your presentation, that seems to be moot. There seems to

be some question as to whether that can be done or what the interpretations might be.

MS. ROSENFELD: At the moment, it is not being done and I think the vast majority of opinion is that it cannot be done. As I indicated, there's at least one and possibly two or three other people who believe that this is a legal theory which has some merit. But so far, it has not been translated into any kind of practical application.

DOCTOR RUDDLE: Yes. Because that would be the thing that would worry me. Someone could study a part of a genome and then place some restrictions on it because they have already done that. If that's not the case, then I see that the situation is a lot brighter because it means that another group who wants to make the information freely available to the public can go ahead and do so.

So, there can be sponsored programs, sponsored by the government, sponsored by foundations, sponsored by universities and even by commercial groups which would do this work and then make it part of the public domain. As long as

there's no compulsion not to do that, then I think the situation is a fairly good one.

CHAIRMAN LOWRANCE: Let's pursue this just a minute. There are a couple of hands up down in the lawyers' corner.

Mr. Caskey, if you would -- let's stay on this point for a minute and then I'll broaden back to Doctor Caskey.

MR. KARNY: Okay. The copyright or can I get into the whole human genome ownership question too?

CHAIRMAN LOWRANCE: Why not.

MR. KARNY: Okay. That's really the copyrighted part of it.

As Charley Van Horn mentioned before, one of the basic concepts of the patent law is it's got to be new before you can patent it. It's got to be novel. The human genome is not new and it's a so-called product of nature. It's not going to be patented per se. An individual gene is not going to be patented itself. It's not going to meet the requirements of the law.

And if you want to just get away from the technical requirements, just think about it. Patents protect something that an inventor comes up with and gives to the world. So, the gene, per se, is already there.

Now, if I take a gene that does one thing and half of a DNA sequence that does one thing and put it together with half of a DNA sequence that does something different and come up with a totally unexpected protein product that is something wonderful, that does who knows what, now that's going to be patentable and I think it should be patentable.

Again, but for my actions, but for my work and activity, that wouldn't exist. So, I think there is a distinction.

Now, to address the copyright issue for a second --

DOCTOR RUDDLE: Could I intervene just a second before you get to that?

MR. KARNY: Sure.

DOCTOR RUDDLE: I don't want to throw you off the track, but there's a kind of a middle ground

in what you're talking about in regard to the RFLP. That's also a product of nature. It's already in nature. It has to be described. It can then be used for a diagnostic test for a particular disease condition and I presume that that is being patented. So that is a kind of situation that comes sort of in between making a construction or change in the material and just simply reading the material.

MR. KARNY: Yes, that's a good example. The method clearly is patentable.

DOCTOR RUDDLE: Yes. And I think you would agree that it can be patented and it has been.

DOCTOR ALFORD: Right.

MR. KARNY: Or is being.

DOCTOR RUDDLE: An interesting question with regard to that is if you are able to patent it, are you in a position to interfere with the use of the RFLP diagnostic test in a nonprofit situation, such as a clinic or can you influence the use of that information or that situation with regard to teaching or further research? I think that's another interesting question.

DOCTOR ALFORD: That's a very interesting question.

DOCTOR RUDDLE: I don't want to throw you off the track with regard to that.

CHAIRMAN LOWRANCE: Mr. Karny, would you finish your general comments?

MR. KARNY: Okay. Those are good points. We ought to really discuss that.

Again, on the copyright issue, I think there are some interesting arguments that can be made for copyright ability. But I think basically, one of the requirements with regard to the copyright law is this idea of originality. Again, simply fishing out a DNA sequence from the human genome doesn't seem to me to meet the requirement for originality. I can't see that thereupon giving somebody some type of copyright.

Now, if you take Herb Kayton's argument and maybe play around with the sequence, perhaps there's something there that can be copyrighted. But in terms of the protection that it gets somebody, I certainly feel that it doesn't get you very far.

Somebody else can do exactly the same thing and get something that's somewhat different. It's an original work and they can go ahead and use it.

So, I don't really see copyright as stifling research in this area. But I do think it's certainly something that can be looked at in a lot more detail.

CHAIRMAN LOWRANCE: Okay.

Other comments on this strict point? I do want to turn to some other ends that were up.

Doctor Caskey?

DOCTOR CASKEY: Well, I'm put very much at ease that the information cannot be put under copyright. That makes me a lot more comfortable in this discussion.

I've been thinking about a point that Leroy made a little earlier there. When we go back in history and look at some things that we've done and whether we did them right, there's a little bit of guidance to what we should be doing in this area.

I would point to the area of recombinant DNA technology. There are many people who would feel

that we made substantial errors in the way in which we handled ourselves, having developed this very powerful technology in the United States. We developed a technology and immediately put the brakes on. The brakes we not applied elsewhere at the international level. Fortunately for the United States, we were able to maintain the leadership with the technology, maintain public faith and did not lose the ball game.

I think that we could be in a situation now in this country in which perhaps the threat may not be coming from the biological community that almost blew it, but possibly the regulatory aspect. All of us who work in this field have enjoyed tremendously this catch word of "cloning by phone."

We had Japanese people from the National Academy visiting our center three years ago who had never heard the catch word. Every molecular biologist in the United States has known "clone by phone" for years. The communication and exchange between investigators in the United States has kept the research at an extremely high tempo. The

exchange rate has been extremely good. The cooperation level, I think, has been really outstanding. I think the system is tightening up.

CHAIRMAN LOWRANCE: You might explain what that term meant for those who --

DOCTOR CASKEY: Well, Professor X at Stanford has something that you've heard about at a Gordon conference or a meeting and it would greatly facilitate your research in an area that is probably not identical to his own interest. You ring up the professor at Stanford, the next day in the mail by Federal Express comes the clone and you're off and running. You've cut back nine months, 12 months of developmental work and you're immediately moving on your project.

That's been going on in the United States at great speed and has accelerated the biologic applications of a lot of our technology. I am definitely detecting, as I call my friends now and discuss these things, a tightening of this attitude. I would like to see us focus on ways of facilitating the exchange of information materials. And if we

have cumbersome old patent laws that aren't staying up to speed with the speed of this technology and science, then let's rewrite it all, let's get it straight, let's maintain the leadership, let's facilitate these actions.

But I think if we add more and more burden of regulation on here, we'll kill this whole gem, in a regulatory way, the way we almost killed it biologically when it was first developed.

CHAIRMAN LOWRANCE: Patricia Hoben, do you have a comment at this point?

DOCTOR HOBEN: I just wanted him to clarify something, which he did.

CHAIRMAN LOWRANCE: Doctor Alford, I wonder whether you would -- we raised some issues with you a minute ago. I wonder whether you could extend them just a little bit.

DOCTOR ALFORD: I think what Frank Ruddle asked me is once the first diagnostic test is actually patented, what would a company such as mine do with that? Would we have everyone cease and desist those kinds of testing, that kind of thing?

It's obvious that we're not going to do that kind of thing. I'm glad that LeRoy Walter brought that up.

It will be similar, I think, to what's going on and what we've been doing with just the recombinant DNA. We've been sharing our clones and we're careful how we share them, make sure we can retain some rights, but I think once, for instance, if there is a granting of a patent for a specific diagnostic test, one will probably offer licenses to non-commercial entities, for one. But I don't think that we will hinder at all any kind of research activities, clinical diagnostic activities.

Right now we have collaborations with clinical diagnostics with hospitals that are doing clinical work. So, I think that's what you're asking, Frank, if I'm correct.

DOCTOR RUDDLE: Sure.

DOCTOR ALFORD: If we were to do anything different, then we are stifling it.

DOCTOR RUDDLE: And I don't mean to be critical of your organization, per se.

DOCTOR ALFORD: No, I appreciate that.

Yes. We can't, I don't think, because it's an ethical question. I think it's also a business question, in part. We would not stifle these things whatsoever in the scientific advancement.

With the SEF, I love that example. We found out on Monday and we announced about it on Wednesday because that was the first meeting we could get a full kind of participation in. And so, I hope that we will continue to do that and operate in that fashion.

CHAIRMAN LOWRANCE: LeRoy Walters?

DOCTOR WALTERS: There's another example from the recombinant DNA history that may be instructive and that is what happened with the Stanford/UCSF patent on a certain plasma. I'm not in a position to sort out all the details of that history, but there were years of uncertainty about whether a plasma combined with some new DNA could be patented, could not be patented, under what circumstances it would be shared and would not be shared.

Has that full type of situation been

clarified by either practice or by legislative refinements since that time or could we get into the same kind of situation with mapping and sequencing of the human genome? With uncertainty about what is patentable and what is not, are we likely to get into the same kind of morass again, but with different materials?

CHAIRMAN LOWRANCE: Mr. Van Horn, do you have some comments on that for us?

MR. VAN HORN: I believe the answer is yes, we're likely to do that.

DOCTOR WALTERS: Get into a morass?

MR. VAN HORN: Yes, in terms of what is patentable and what is the scope of the enforceable right, in that particular case there was a long period of time when that application was pending before it ultimately issued as a patent. And right now, we're experiencing the same kind of difficulty. Back in 1980, we had about 300 applications. Now we have about 6,000 pending applications.

In some areas, in the recombinant area, we're looking at almost 26 to 28 months before a

patent examiner first picks up the application for examination purposes after it is filed. Yes, that's a problem.

CHAIRMAN LOWRANCE: Are there structural difficulties that could be focused on in the next few years in addition to hiring more patent examiners or things of that kind? Was it rewriting of law, new guidelines?

MR. VAN HORN: No. We have to recognize too that the office has a position in this whole process. He can make a determination, but indeed the marketplace and the courts will openly determine what the rights are.

In that particular case also, there was some dispute about, even when we issued the patent, whether it should be issued or not. But they had a very favorable licensing agreement and a lot of folks signed up.

CHAIRMAN LOWRANCE: Currently, there's a lot of debate over the patentability of mammalian forms. Is that going to have implications for human genome projects?

MR. VAN HORN: I think there's some uncertainty there, yes.

CHAIRMAN LOWRANCE: Doctor Cozzens?

DOCTOR COZZENS: We did point out that the point of the patent system is to make information publicly available, but during the application process, is it or is it not publicly available? Can anyone go in and read your patent application or is that complete private?

MR. VAN HORN: That's correct.

DOCTOR COZZENS: So, you have to wait until you find out whether you've got a patent or not.

MR. VAN HORN: It also frees up the individual or the organization who has filed that particular application, once having established that proprietary interest in filing the application, to publish without losing any rights. But the application itself is not public.

DOCTOR COZZENS: But as long as there's some question about whether a diagnostic technique, for instance, is or is not going to patentable, then other people cannot use it or they use it only at

risk of later violating the patent. Is that true?

MR. VAN HORN: That is correct, yes. That has no enforceable right when it's pending, only after it's granted as a patent.

DOCTOR COZZENS: As you point out, then the information is there, the scientific information, for instance, could come out as soon as the application is filed.

MR. KARNY: If the applicant does it.

DOCTOR COZZENS: Right.

MR. KARNY: It's up to the applicant. If the applicant desires, they can keep that information non-public. Generally, in most instances, they feel secure enough when the application is on file that they will ultimately get some fair amount of protection and they will publish. But there may be instance where you don't feel secure about that, for whatever reason, and it won't be made public. So, there will be that period where it could not be disseminated.

MR. VAN HORN: In countries foreign to the United States also they have a policy and practice of

publishing the application, contents of the application 18 months after it is filed, after the initial priority date, regardless of the determination of patent rights. So, if you're dealing in the international marketplace and you're filing not only in the United States, but also in a country foreign to the United States, Europe or Japan, they will publish the contents of the application 18 months after the original filing date.

CHAIRMAN LOWRANCE: Doctor Walters?

DOCTOR WALTERS: What would a prudent clinical laboratory do in the interim after the application is filed by your firm? When the patent application is pending and if they wanted to use the technique that you had developed, could they write to you and ask for permission to use this on an experimental basis in that interim? What can be done??

DOCTOR ALFORD: I guess many things can be done. If I've announced, for instance, a diagnostic test and you have maybe some probes, you could probably practice it yourself without even having to

contact me, could you not? Maybe you're asking the question if I have a diagnostic test, that you don't have any probes for and that you want to practice that diagnostic test and maybe you learn more about the gene itself or the locus itself. Then you should contact me.

What I've done and what we've been doing is -- I'd be glad to set up a collaboration because I'd like to learn more just as you'd like to learn more. So, maybe you'll share your patients with me or your samples and I'll share my probes with you. So, it's that kind of thing that will be set up. That's the initial thing I think I address earlier, is how is the best way for us to do that together? How can we share it together? There's no question that what you want to do is probably contact me if you do not have the tools yourself in your own laboratory.

If I announce, for instance, a diagnostic test and its linkage to a specific disease gene and you don't know what chromosome it was one until I announced it, then you're going to probably rush to look at what probes and what information you have

available on that particular chromosome and you may come up with something that's very similar to defining what I just announced.

CHAIRMAN LOWRANCE: Susan Rosenfeld?

MS. ROSENFELD: I just wanted to get some clarification. When you make a probe or something similar available for purposes of research, would you do that under some form of restricted use agreement, an actual written agreement? You wouldn't just send out the probe with no conditions attached relying upon the investigator, or maybe you would.

DOCTOR ALFORD: What one usually would do is attach an agreement to it, an agreement for restriction. You have to remember that I, as a company, have an obligation to my investors and I have to protect my investment. But by protecting my investment, I'm not just going to keep it to myself. I want to be able to share.

The only way I could share is by giving it under a collaboration. We're going to work together. I'm not going to restrict you from any of your experiments obviously, but I would ask that you not

give it any further. If you have any contacts that would like to also receive it, then please have them notify me. That's what I try to do usually.

There's many different, of course, arrangements that can be set up. There's a multitude of different kind of arrangements, but that seems to be a popular one and that's one that has worked for us many, many, many times already.

MS. ROSENFELD: When you have these kinds of agreements, do you ask that if the investigator should come up with a new invention or a new use or a modification of the probe, that they give your company any kind of rights with respect to that new development or do you not address that?

DOCTOR ALFORD: Sometimes we do and sometimes we don't. It depends on what the initial structure of the agreement was. It depends on what the materials were. It depends on what that investigator is seeking. It depends on the particular agreement what the company is seeking. That question is very hard to answer. It all depends on what the initial structuring is and the initial

intent was and what the initial goal is for both parties.

There's some, of course, investigators that we will speak with who really don't care anything about any kind of commercial benefit whatsoever. They don't want to be hassled with that. All they want is just getting this. "Just give it to me for a month." That letter agreement that I'll have with that person will be very short and sweet because there's no reason to get in any kind of details.

But there is the other person who's very cautious. He's very concerned that he has government funding, what impact will that have if I share with him, what rights will that be and that becomes a little bit more involved and a little bit more cumbersome. So, it's all according to each specific case, really.

CHAIRMAN LOWRANCE: Other general comments? Yes, Mr. Gould.

MR. GOULD: I'd like to go back to an earlier statement about a concern raised about the potential for patenting rice or something along those

lines. I think there has been continual scare attitudes based on that kind of a concept that somebody's going to really dominate or take away the ability to grow or produce important foodstuffs or animals, et cetera.

I really think that that's a misconception. What people are really talking about is patenting and obtaining rights to an invention relating to rice. That is there was an improved rice that has a certain characteristic which embodies a very specific invention and that's what is being alluded to.

I know, for example, that the University of California gets its major licensing revenue from the sale of strawberries. They have obtained patents to an improved strain of strawberry. I sleep very well knowing that these people are out there getting revenues from strawberries. I continue to eat strawberries and they continue to be made available. So, I don't see what seems to trigger such an adverse reaction to the ability of people to do that.

DOCTOR COOK-DEEGAN: What about the situation of Kodak/Polaroid, where it seems like one

of the things that case turned on was an array of patents around a process that essentially was impossible to penetrate?

MR. GOULD: You have a patentee who was able to protect a very substantial investment in a new technology which they pioneered. I don't think anybody has real trouble saying that for the 17 years that the patent system gives them the exclusive right to practice that, that they should have that right. I think somebody who tried to enter into that prematurely got tripped up. I think that was a very pro-patent statement by the courts and probably is a strong incentive for others to continue to invest in developing new technology.

CHAIRMAN LOWRANCE: Let me just ask, it's about time for us to break in order to get to lunch on time. Be thinking whether you have any final comments, that is up to lunchtime.

We haven't touched very much on the international dimensions. As I was looking back over our outline, I think we want to be sure to touch on that sometime during the day. We talked a little bit

about the complications if one becomes involved in filing patents in other countries. Are there other aspects of collaboration transborder that will raise complications that might be addressed here?

DOCTOR RUDDLE: Maybe I can go back to the original discussion while people are thinking about that point.

I think the discussion this morning has emphasized how important information regarding the human genome has become. We see it has a dollar value that companies or groups that work out the sequence analysis of certain parts of the genome or develop overlapping configs for certain parts, not all will necessarily be given access.

A company will want to collaborate with regard to a specific kind of disease, say, that may have some commercial application. But someone who's interested in the basic problem, which has no commercial application and which may serve to disseminate that information more than the company would want it to be disseminated, that that individual may be locked out from that information

for a period of time.

I think that's why it's all so important that there be a government sponsorship of analyzing the genome and with the understanding that that information, as it comes out, is placed in the public domain where it is available to all the scientists in the country and the world who need that information to carry out their basic research.

CHAIRMAN LOWRANCE: Other closing comments before we adjourn?

MR. GOULD: If I may, I think Tom Caskey made a very eloquent statement earlier about the need to mobilize and get the proper momentum and incentives for a program of this dimension to succeed.

In looking at the international arena in biotechnology, one sees, for example, the ability of Japanese companies to be organized and focused by the government and with the government assistance and to develop the technology so rapidly so that within five years -- whereas at the time we started the biotechnology development, Japan was a net importer

of our technology and licensing in substantial amounts of technology.

Today, I think it's not uncommon to find license agreements by American companies licensing back from Japan new aspects of this technology. I think that if our government wants to focus this effort, they should provide the necessary incentives in similar fashion, to allow companies to get together, to allow companies in academia and the government agencies to work together in a very positive way to try to achieve this goal.

CHAIRMAN LOWRANCE: Thank you.

DOCTOR COOK-DEEGAN: That does raise another set of issues and I wonder if we could save that for the afternoon, but I'm interested in what you see as the main obstacles in American procedures. If you could just address a comment to that this afternoon about how can we do that, what federal laws are involved and how does we deal with that question.

CHAIRMAN LOWRANCE: Bob, tell us the logistics on lunch.

DOCTOR COOK-DEEGAN: We need to get down to

those folks who are on the panel and those who are presenting this afternoon and a few other people who have already contacted me or some other people at OTA staff are invited to this lunch sponsored by Hughes Medical Institute. It is in room D369 in the basement of this building. I don't know the exact map for how to get down there, but if you go down the elevators, on every floor there is a diagram of where the room numbers are. So, we can meet down there.

Those of you who are not on the panel or presenting and have not notified us, there are cafeterias in this building, in the Cannon Building next door and in the restaurants around this area.

CHAIRMAN LOWRANCE: We'll reconvene at 1:15. We're privileged to have some very busy people meeting with us this afternoon and we would like to start at 1:15 if we can.

(Whereupon, at 12:10 p.m., the meeting was adjourned to reconvene this same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:20 p.m.

CHAIRMAN LOWRANCE: After a very interesting discussion this morning, we now have a chance to take sort of a cross cutting examination as we invite representatives from three federal agencies, one from Howard Hughes Institute and one from the NAS Committee responsible in this area to make statements of their activities, concerns.

I would urge the presenters now to raise issues that are of interest or you think OTA might well address in the study that's underway.

I won't do any elaborate review. I would just introduce Doctor Ruth Kirschstein first, if I may, to speak for NIH.

Welcome.

DOCTOR KIRSCHSTEIN: Thank you. I'm on a little bit of a marathon, having talked on drugs at the IOM this morning and genome with you this afternoon.

I think it's clear that it's been several years since all these discussions have started and

that nothing has quite sparked so much excitement as has this project related to the human genome in a long time. I think the thinking of all of us has evolved considerably.

There have been many committees, many meetings on the subject and about nine months ago, the Director of NIH, Doctor Weingarten, held a meeting of his advisory committee and the minutes of that meeting are now available and I think have been distributed to the panel.

For those of you other than the panel, it was hard to carry as many of them as we thought we might need, but Rachel Levinson here has them available and we will be pleased to try to provide them to you.

Since that meeting, a number of things have occurred at NIH and elsewhere. The Director of NIH has now established a working group related to activities on the human genome and it's a working group of the membership at the very highest level of NIH and Doctor Weingarten chairs it personally. So, I think that indicates to you his interest in the

subject. He's also included, above and beyond a number of the Institute director's, a member of his advisory committee, George Palai.

We've taken a close look at the activities that NIH supports in characterizing complex genomes, which is really what I prefer to talk about in terms of the entire project.

One of the things that came out of that Director's Advisory Committee meeting was that those of us who believe that the knowledge is important certainly would agree that the knowledge about a number of genomes is important. Mapping and perhaps sequencing the human genome without doing a number of other genomes will not add enough to our knowledge. So, we've been talking about characterizing complex genomes.

When we've been taking a look at the work we support in this area, we've sort of, in a natural way, divided it into three general areas and I'll come back and talk about some of the specifics in a moment. One is focused research which, for example, might be major projects directed toward mapping or

sequencing an entire chromosome or an entire genome.

Another is research directed toward mapping specific genes, control elements, et cetera. And finally, research in the development of methods, biomaterials, information, which one could call the infrastructure.

We've also looked overall at the research that's supported by NIH and divided into what is done for the human part of the problem and what is nonhuman. And then we've looked at what is done intramurally by the scientists within NIH and the extramural or grant community.

At present, if you take the first definition of focused research as being major projects directed toward mapping or sequencing an entire chromosome or an entire genome, there's very, very little activity that NIH supports that's that narrow. Almost all of the research is much broader and in that basic area, somewhat over $300 million a year is expended by NIH in 1986, of which about $203 million was for characterization of nonhuman complex genomes. And about $91 million for human genomes.

There's another $55 million, approximately, in what we're calling the infrastructure.

In 1987, this current year, we would expect that to be a little bit larger, going up to about $216 million for nonhuman work and about $100 million for human studies.

Of the research, about $45 million in both '86 and '87 is expended intramurally by the scientists who work in the intramural program at NIH and the remainder is primarily in grants with a little bit in contracts.

Now, as David Kingsbury may tell you in a bit, we've also been attempting to develop interagency coordination of all our efforts. And at Doctor Kingsbury's request, Doctor Weingarten is chairing an interagency group. This chairmanship will rotate so that next year probably someone from the Department of Energy will chair it.

The participating groups are the Department of Energy, the Department of Defense, EPA, FDA, USDA and NSF. They will also each be asked to provide information related as I just gave you so that a

working group on biotechnology, which Doctor Kingsbury chairs, can report to the Domestic Policy Council about this. Any project that's as large as this clearly begins to be of interest to very high levels of the federal government.

We're going to ask private organizations and foundations to also tell us what they're doing. So we will hope that we'll have an overall view of the situation.

As you know, the spring issue of the journal called Issues of Science and Technology had a number of articles which I think at the last meeting Bob Cook-Deegan handed out and several of us were asked to prepare letters. I had a letter in the summer issue expressing what is NIH's position on this and also giving summary of the recommendations that came out of the Director's Advisory Committee. I would assume that you have copies of that too because I sent them down here.

And on May 29th, we published in the NIH Guide to Regs. and Contracts, two program announcements that were worked up by a working group

representing the staffs of most of the institutes. The primary people who worked on this were Irene Extrand, who's sitting here, and Rachel Levinson and then a number of us looked at it.

The two program announcements are related, one, to a process of analysis of complex genomes to development of new technologies, methodologies, new restriction enzymes, new ways of cloning large fragments, new vectors, et cetera, real basic research. The second one is related more to what we're beginning to call the informatics area which is how to improve computerized manipulation of the data as it's generated by molecular biologists.

Now, these program announcements are just that. They are not requests for applications. A request for applications has to have a specific sum of money allocated which says that if the research is of sufficient scientific merit, the organizational entity, or at least the way NIH uses it, will extend that sum of money.

We decided that that was not what we wanted to do. We really wanted to encourage research and

see what came in in that regard. So, we did not put any specific sum of money on this.

There is not this year in NIH's budget any new monies that can be expended. You can see that there is a very large amount already being expended. But we have, by the program announcements, essentially pledged that we will do something. As we get applications, we will choose the best ones based on scientific merit and relevance and depending upon to which institute they're assigned, we will fund them.

We are beginning to get some responses and inquiries and we expect considerable interest. We have heard from several people who have some ideas that have made us think that it would probably be worthwhile to hold several technical workshops where we will have people come out and actually talk about ideas they have for doing things. Probably the first one will be sometime in the fall.

That pretty much summarizes where we are at the present. I'll be glad to answer questions.

CHAIRMAN LOWRANCE: Thank you. That's very

succinct.

I wonder if anyone here would like to ask questions of -- problems in collaboration, restraint -- several times this morning people did raise questions about whether NIH and other agencies were placing constraints on sharing of information coming from these programs.

DOCTOR KIRSCHSTEIN: No. NIH will not place any constraints on sharing of information. We expect our grantees to share such information in the ways they have in the past.

I can tell you that in years past, when a study section which is an initial review group made up of scientific peers of the people whose applications are being reviewed, has found in a grant application, or has evidence from things that have happened, that a particular individual, group of individuals, university, company, etcetera, is not willing to share a new clone or a new organism or something of the sort, that is discussed in great detail and certainly, as you know, the second level in review is the National Advisory Council and my

council, at least, will suggest that we not fund such work until that can be straightened out.

So, there would certainly be very free sharing of this. It is of interest that we plan to do some sharing in ways that perhaps have not been done in the past. We are currently, for example, in a related area, reviewing some grant applications, launch program project applications, to an announcement that was put out for studying the structural biology of the AIDS virus, specifically because of targeted drug design.

We intend for the people who receive those awards to meet together regularly to share information, because we feel that that project is so important that whatever is found needs to be shared very very quickly. So, we fully intend to have everything hanging out and freely available.

CHAIRMAN LOWRANCE: Again, just thinking back through this morning's conversation in which there were suggestions that in the past, not necessarily at NIH, but in the development of cell lines and things of that kind, there's been some

ambiguity in the law or the funding auspices in how the material is to be shared or how fast.

I wonder whether you've considered -- maybe you've already prepared guidelines on sharing of information, materials, and so on, coming out of this area?

DOCTOR KIRSCHSTEIN: Well, since I said that we feel it should be shared freely all the time, I don't think we really need them. There is one place where there has been something fairly interesting that could be possibly applicable and I think I need the staff of the genetics program to help me a bit, but I think I'm correct, one of the resources that NIGMS supports is the human mutant cell repository, the cell bank.

I believe that when a scientist is approached and does finally deposit cells from an individual with a particular genetic defect or something of the sort about which he has not yet published, we give them a years period to work things up to publish before we generally make it available.

CHAIRMAN LOWRANCE: How about the

constraints on the donor. Again, following up on this morning, a question came up, "suppose someone's own tissues are become a source?" Is that --

DOCTOR KIRSCHSTEIN: Well, that, of course, is something that you people have just written about and the Cancer Institute has had a great deal of experience with. I expect that that's going to end up more and more in the courts.

DOCTOR BERGMAN: There's one very specific restraint --

DOCTOR KIRSCHSTEIN: This is Doctor Bergman, from the Genetic Department.

DOCTOR BERGMAN: -- which may be of interest. We request that before material be supplied in human experimentation that we be notified as planning officers, and then we have a very thorough review ourselves and insist that there be a thorough review before it can be used for those purposes.

CHAIRMAN LOWRANCE: Review of what?

DOCTOR BERGMAN: Review of the protocol for which they're using this material.

DOCTOR KIRSCHSTEIN: In humans.

DOCTOR BERGMAN: In human experimentation.

DOCTOR COOK-DEEGAN: For the transcriber, that was Fred Bergman, of NIH.

CHAIRMAN LOWRANCE: Other questions from around the table for Dr. Kirschstein?

DOCTOR WALTERS: This is just a simple conceptual question.

What is excluded by the notion of complex genomes?

DOCTOR KIRSCHSTEIN: Bacteria, I guess. No, not really. I think it's simply a way of saying that we want to broaden it beyond human. Possibly viruses would be excluded, but not necessarily.

CHAIRMAN LOWRANCE: Let's go on then, at this point, if we may, to Doctor David Smith, if you will.

DOCTOR SMITH: Thank you.

Just a few brief remarks to summarize what we've done at the Department of Energy, and a little more specifically, try to raise a few issues related to the development of what we're calling a physical

map of the human genome.

Following a workshop which we sponsored which was held in Santa Fe, in March of 1986, the Department proposed a coordinated, focused effort to create the technologies, the tools, and the resources which are necessary to achieve a complete characterization of the human genome at the molecular level.

We proposed that the first phase of this project should have three goals and the first phase would probably last several years. We were estimating five to six or seven years.

The first of these goals was to prepare a physical map of the human genome. By that we mean an ordered, cloned, overlapping DNA fragments which represent, ideally, the entire human genome. And furthermore, the placing of this physical map in a repository where the DNA fragments could be accessed by everybody, perhaps, or perhaps that needs to be thought about.

A second goal was to develope the innovative new technologies which would greatly

increase by orders of magnitude, the speed of DNA sequencing and related molecular biological manipulations and also decrease the cost by several orders of magnitude.

As a sequel to that, we've felt all along that the decisions regarding full scale sequencing should be deferred until the technology justified such an approach.

A third goal had to do with developing the informatics tools which are needed to handle the rapidly increasing data in human genome and genomes in general, algorithms, analytical tools, better data bases, networking, automated data entry, all of these things and a wide variety of needs that have been addressed by a number of conferences.

We had an advisory committee which looked into our proposal and has prepared a report. Bob has a copy of that. I did not bring copies for the panel, but I can certainly get them to you in a day or two if that's required.

DOCTOR COOK-DEEGAN: We'll keep a list. If anybody wants the DOE report, I'll just make a list.

Just tell me after the meeting, or during.

DOCTOR SMITH: But rather than go into more details about what we're proposing, I would like to just talk a little bit about this physical map and what's entailed in the physical map and some of the issues which need to be considered.

Most of you may be aware that the Department has been supporting the development of chromosome specific DNA libraries developed at both Los Alamos and Livermore. These libraries are housed and distributed in a repository here in Rockville at the American Type Culture Collection, and this repository is funded by the National Institutes of Health.

We believe that a similar kind of collaborative arrangement makes a lot of sense for this physical map that we're proposing to develop. As you're probably aware, a physical map of this type will consist of tens of thousands of DNA fragments and creating an effective repository to keep track of and to store and to replicate, to distribute these tens of thousands of fragments is not a trivial task.

And that's just the physical handling of these fragments.

In order for this repository to be useful, there also needs to be an associated database. For each of these fragments, we need a lot of information. We need to know the source of the fragment, the source of the DNA, the cloning vectors that are used, the genes that are on that fragment, the proteins that are coded by that fragment, the introns, the exons, the other genetic markers, the sequence information associated with that fragment, everything.

And this has to be updated regularly if people are going to make use of this. That implies that this database must interface very effectively with other genetic databases, or else this information must be appropriated into other genetic databases. That itself is a very major task.

You want to interrupt?

DOCTOR COOK-DEEGAN: Just to follow-up, I don't want to stop there. I wanted to get a little bit of clarification.

Are you suggesting that you would use exactly the same methodology or an analogous one like it? Would you send this to ATCC?

DOCTOR SMITH: I'm not identifying any place.

DOCTOR COOK-DEEGAN: Okay.

DOCTOR SMITH: But I'm saying that a repository needs to be established.

DOCTOR COOK-DEEGAN: Okay.

DOCTOR SMITH: And we are proposing -- we have been talking with the Division of Research Resources, who fund the library repository, about sitting down in a workshop to discuss the needs and how to go about establishing such a repository.

Physical mapping efforts are underway. It's a little hard to predict how soon ordered fragments will be ready for a repository, but it's not too soon to begin thinking about how such a thing should be set up and organized. So, we are organizing a workshop with the Division of Research Resources that may be held later this summer, although I'm not entirely positive about that.

But it's clear that some very serious thinking needs to be undertaken about how this should all be pulled together. There are a few issues that, I think, were probably raised this morning and I certainly don't have any -- not only not any special expertise, but probably not any expertise about intellectual property, but the question of access to this repository is a very key one. Should it be entirely open to the public, to the entire world? Should it be restricted in some way? What kind of fees should be charged? I don't have the answers to that, but I think that these are questions which need answers.

CHAIRMAN LOWRANCE: Do you have a group addressing those at the same time you think about the physical problem of the logistics of pulling it off?

DOCTOR SMITH: We have not set up such a group and have not talked about it.

The other questions, to what extent can we legally require -- what arrangements should be made? If we fund somebody for ordering DNA fragments, can we be assured that those ordered fragments are

immediately put into the repository? To what extent should the people who are doing the ordering be allowed to make use of them for their own purposes, which may be a separate and divergent from the needs for a public repository.

It would be a real serious problem if we use government funds for ordering and we can't be assured that those ordered fragments end up in a government funded repository.

As you're aware, there are, both in the public and private sectors, people who are developing genetic markers, particularly RFLPs, that are very, very useful in this ordering project. To what extent can we make use of private sector genetic markers to help us in the ordering of these DNA fragments without compromising the proprietary rights of those companies. There are a number of these issues. Can we, in fact, make use of those genetic markers. I think in some cases they could be very useful.

So, those are just a few of the issues that need resolving. I hope you do that for us.

DOCTOR COOK-DEEGAN: We'll have it done

tomorrow.

CHAIRMAN LOWRANCE: Some questions for Doctor Smith? He's already raised some of his own questions and preempted us, but are there other questions from around the table? No?

Let's move on then to Doctor Kingsbury, speaking for NSF, and maybe other groups.

DOCTOR KINGSBURY: Actually, I'll really focus on NSF activities for the most part.

As some of you have heard me say before, the focus that the National Science Foundation has is not on mapping the human genome. That's something that we feel is outside of our sphere of activity. We aggressively stay away from things that we view as being clinically oriented and we do human related biology, there's no question about it, but we take a very extraordinarily fundamental scientific approach to it.

So, we have a number of activities that would fall into the sphere of the complex genomes. Well, I'll define complex genomes as eukaryotic genomes rather than -- not to say that E. coli is so

simple, but let's stay with eukaryotic genomes.

Certainly, I think that it's fair to say that the National Science Foundation supports a great deal of fundamental research in nonhuman genome mapping, especially in plant sciences, plant genomes. We have put a great deal of emphasis on plant biology in the past few years, continue to do so and have supported a number of people that have been working in plant systems, particularly maize but other systems as well.

Likewise, we've been interested in the mouse genetics and areas related to mammalian genetics, not human. So, I think we're pointing out that we do have some real interest there. It interfaces very well with the human genome related research.

In the case of some of the simpler genomes, I think it's worth pointing out a couple of things that we do have going because I think they're very relevant to this question. We have to start at some baseline level and build up in terms of how we keep track of what we know about various genomes.

For some number of years, we've supported the E. coli mutant collection at Yale University, which is run by Barbara Bachman and Ed Addleburg. There, we've been focusing in the last few years and will continue now with even greater emphasis on pulling together the entire data resource related to that genome.

That is that we now, from Columbia University, have what appears to be a nicely developed and still expanding physical map of the E. coli genome and even just as much as last week, George Church from Harvard has reported at a Gordon conference that he's now sequencing E. coli at the rate of 50 kilobases a day, I understand. He still believes that he will have E. coli and salmonella typhimurium completed by the end of this calendar year.

Well, you can see that this is the prototype for the kind of thing that we've been talking about for a year and a half in the human, a series of genetic markers, a physical map and a sequence. So, we are going to attempt to continue to

support development of a database that's related to that.

So, let me just break this down as an example of the kinds of things NSF sees ourselves doing, is interfacing in the areas of technology development for sequencing and handling those sequences. An example is the semiautomated sequencer developed by Lee Wood at Cal Tech which is now being commercialized by Applied Biosystems. That was an example of something that was at least partially supported by NSF. The continued development of that kind of activity is still going on under our support.

Because of our close relationship to computer sciences, which is done within NSF and actively done information science and basic computer science, we feel that, again, much like DOE and some of the things that Doctor Kirschstein mentioned, informatics, algorithm development and information handling is something that we have a focus on. We're trying to do this in collaboration particularly with DOE, but certainly with anyone else.

I should mention at this point that we have

a formal relationship with the Department of Energy. NSF -- across the board, at all of the NSF divisions have close working groups with DOE because of various levels of overlap. The biological sciences is included in that with two working groups, one in molecular biology which includes this kind of what we're talking about here, and another one in environmental biology. So, that kind of focus is one that we share.

Again, NSF's focus on nonhuman genomes and the general infrastructure. We have an aggressive program for buying instrumentation for the research community. We've just gone through a series or a competition for some facilities oriented research centers and that competition will continue to go on. It's not oriented toward the genome, but it's not oriented away from the genome. You compete on the basis of good science.

So, I think that really that summarizes our approach. The kinds of things that Doctor Kirschstein mentioned in terms of new restriction enzymes, chemical methods for directed cleavage is

work that's been going on under NSF support for some time. And we don't have any reason to believe that we'd discontinue that kind of orientation.

Now, let me just make two other comments. If you ask questions about the DPC Working Group Coordinated Report I will answer them as best I can. I'm not going to say anymore than what Doctor Kirschstein did. She seems to have described it much more eloquently than I can probably. There has been a focus on agency coordination and that is still something that we feel strongly about and are continuing to do.

I'd like to make a couple of comments in just related activities in terms of data sharing and requirements for data sharing and precedents for that. As many of you know, my little world at NSF includes the social sciences. The social scientists, of course, live on databases. We see a situation where much of the empirical research that we support is really the development of a database that an investigator or a small group of investigators would use for a particular project.

One of the concerns we had was what happens to those databases and once that project is completed, does it then go out of existence or does something else happen? Over a year ago, we implemented a requirement for establishing a database repository so that that data had to be made available as a condition of an NSF grant.

So, I throw that out as a paradigm that is in place and so far our general counsel has supported this as being a legitimate requirement. After some squirming in the initial stages and some discomfort, once we took the bunsen burners away from his feet, he agreed. So, we now have that in place.

Another thing that we have discussed doing, and this is not something that we have in place right now, but it is something that we've discussed, is it part of the regulatory world. One of the things that people who are currently working in the area of environmental introduction to microorganisms have been concerned about is the restrictions on certain kinds of constructions of microorganisms that are the result of organizations that may have come from

having been plant pests. This puts that now under the Federal Plant Pest Act and could become very restrictive in terms of the ability to use these organisms.

One of the concerns has been how can we quality an exemption for a particular organism? For example, an agribacterium or TI plasma and cloning vector and how could we exempt that because it's been disarmed.

Here was a situation where, as we have thought about it, I think their method of going ahead will be to allow the Agriculture Department to approve a disarmed vector which then would fall out of the regulatory net based on the condition that that vector is in a public repository and freely available. Only under those conditions would it be considered an accepted disarmed vector. Then, of course, the implications are that everyone who used it would use it with the same terminology.

So, that's another model for this idea of public sharing. We probably will be talking to Bob Stephenson about putting aside a little place at ATCC

to put these things. We don't know how many there will be, but anyway, some kind of --

So, I think with that, I'll stop. If people want to know about the coordination effort, I'll try to fill them in.

CHAIRMAN LOWRANCE: Questions for Doctor Kingsbury?

MR. GOULD: Do any of these collaborations extend outside the U.S.?

DOCTOR KINGSBURY: At this point, most of the existing collaborations are within the U.S. I can't think of anything that we have going right now that's international. It's hard to always know exactly how our investigators are doing things. That's the best I can say. We're not aware of any.

CHAIRMAN LOWRANCE: Any questions?

We need to move on. Ms. Kumin, from Howard Hughes Medical Institute.

MS. KUMIN: Doctor Cahill has asked me to speak today on behalf of the Institute. I thought first I'd fill you in on exactly what the institute's involvement is in the human genome projects.

There's three types of involvement, basically. The first type is database involvement and that is composed of Doctor Ruddle's human gene mapping library, which is in New Haven and consists of five databases. It also has access to another database which is OMIM, otherwise known as Online Mendelian Inheritance in Man, and that is under the direction of Doctor Victor McKusick at Johns Hopkins.

There's a second type of involvement which is research being done at the various HHMI units that are throughout the country at hospitals, medical centers and universities. An example of that is the work that's done by Doctor Caskey. Also the work done by Doctor Ray White at the HHMI unit in Utah, University of Utah.

The third type of involvement is one that's basically a collaboration with a non-institute organization. We have an international arrangement with a French nonlucrative organization called SEF. It's a database in France and we now share data through the institute unit in Salt Lake City, the University of Utah.

The Institutes commitment to gene mapping is based on a five year program that was started in 1986. The trustees asked Doctor Cahill to head this five year effort. Prior to the end of that period, in 1991, they'll relook at what's occurred thus far. There's no question but that any federal initiatives at that point will have a great deal of effect on what the trustees decide to do in terms of any future institute efforts in this area.

The Institute's policy in intellectual property as it's applied to gene mapping is basically that the Institute, as part of its chartered purposes, seeks to make information freely available. I'm a lawyer. I've been corralled over here with some other lawyers, so I should tell you that I look to the Institute's charter, and the Institute and its lawyers treat very seriously the directive that we are in the business of making science known and furthering science.

The tension in that policy as it's applied to interactions with commercial and for profit ventures is that while the Institute seeks to make

its information available, it does not intend to allow a commercial organization to make a commercial profit from that.

The example I will try to give you of the different between our permissible use and an impermissible appropriation would be that Doctor Ruddle's human gene mapping library is open and is used by and we encourage use by commercial organizations. Accredited scientists are entitled to dial in, we don't care who they work for. We hope they use that information to further science. We would not allow appropriation of the database itself or any of the five databases for any commercial purpose.

The Institute has, from the point of view of the database aspect of human genome mapping, has some principles that we hope that the federal government would consider in any database efforts.

The first would be that we would hope the information would be freely available, meaning that just as the human gene mapping library and OMIM are freely available, that it would be a venture that

would include commercia, government, academic and non-profit groups such as the Hughes Institute.

We would hope that the lines of communication would be kept open between those various groups and, recognizing the tensions that may exist, that there would be an effort to work with all groups and not exclude any particular group or to make the data available to one group over another.

We would hope that contributors would be making their information available. We would give an example of a permissible kind of a restriction which has an ultimate effect of making information available, our collaboration with this French organization.

The French group gives out genetic material. In return, it asks that information that is the result of using that material be returned to SEF and it agrees to keep that information confidential for periods that are usually no more than one year. We have agreed to respect that one year delay. However, the information is being made available to the Institute.

The Institute is incorporating it in our work and we are then not making it available for this period of up to one year, respecting the necessary property rights and the property interests of commercial organizations who, but for that restriction, might not be willing to give their information back to SEF. SEF, of course, tries not to give out its genetic information without the agreement of the commercial organization to return the data.

So, it should be a two way street and we view a 12 month restriction as not being unduly favorable to the commercial organization. We expect that the information will, once that time expires, then be freely available through the Institute, through SEF and in derivative fashion.

We would also hope, as a third principle, that because the genetic information is being so rapidly accumulated, that there would not be any delay at all in terms of any federal start-up time. I would just give you two statistics that I think will highlight what I mean.

At the human gene mapping library there are five databases. In one of those databases, which is called the probe database, there are roughly 3,000 entries. Over 2,000 of those entries have been updated since the first of this year, and 1,800 of those entries have been updated since just April 1st of this year.

Another example would be that in a second of those five databases, the map database, which has roughly 1,800 entries, 630 of the entries have been updated since the first of the year and 550 and been updated since April 1.

So, if you realize what even a very short lag time would do to those kinds of databases, you realize what would happen if there were any complete halt to not just the accumulation of information, but to making it available through such databases.

And the fourth and last principle we hope the federal government would consider, we don't believe the United States is operating in a vacuum and we would hope that any kinds of database efforts would be done with some sort of international

cooperation or at least an attempt to get kind of international cooperation.

We recognize that there's a history sometimes and intentions, but that isn't a good enough reason not to try.

CHAIRMAN LOWRANCE: Thank you.

Any questions for Ms. Kumin?

Yes?

MR. KARNY: What do you mean by appropriation of the database? You gave the example that somebody could use the database at Yale, but what exactly is misappropriation?

MS. KUMIN: Well, we would consider it misappropriation is someone tried to obtain the entire database and sell it. For example, tried to sell it in a written formal. It's in computer accessible format. Or we would consider it misappropriation of somebody tried to misappropriate the software, tried to take the software and make it available. It's folly because it's updated so quickly.

MR. KARNY: Okay. What they derive from it

on their own, that's appropriate for them to try to protect that if they desire? In other words, they take some information and they get some updated information based upon what they get out of that database. Are they free to use that updated information any way they want, including holding it as a trade secret?

MS. KUMIN: I'm not sure what you mean by updating the information. For instance, in a literature database, you can't update it. It's got bibliographic references.

MR. KARNY: Well, I'm trying to come up with an example. There's databases of some raw material of some kind. Now, if somebody takes that and because of that gets to -- I'm not sure what.

MS. KUMIN: Adds another piece of knowledge.

MR. KARNY: Gets a probe of some kind that they didn't have before --

DOCTOR RUDDLE: We expect commercial entities to be doing that all the time. So, they'll use a database to acquire new knowledge based on

their own holdings of material and information. And that's something we find quite acceptable.

I think what we're concerned about is, say, an entrepreneur who comes in and accesses data from our database, puts it on a compact disk, for example, and then markets that as representation of the current state of the human gene map, which would be, by definition, out of date before it got out.

So, we're a little concerned about something like that.

MS. KUMIN: And there are no conditions put on the use of knowledge gained by access to the human gene mapping library, OMIM, although we would hope that the scientific collaborators who obtain new pieces of information that could update the databases would get back in contact with the medical institute and would allow us to update the databases.

DOCTOR WALTERS: It would seem as if there are significant problems of accounting for something like SEF because different people would draw the line at different places if they were asked to tell what information was developed on the basis of access to

certain materials. I would think some investigators or some commercial firms would have an interest in interpreting that as narrowly as possible and disclosing as little information as possible.

There's no good way to enforce the rule or to go back and check whether they've accounted for what they've developed on the basis of the information they got from the repository.

MS. KUMIN: Well, we recognize that. I guess there are two comments, not really answers. The first is that we just have to deal with that one a case-by-case basis, as lawyers would say, and just look at the facts of that case.

The second thing is the point that George Cahill is always fond of reminding me is that scientists are a fraternity and perhaps the disrespect that a scientist would gain by trying to skirt the commitment that he or she made is far worse than any kind of legal consequences that could flow from that. We would hope that the sense of cooperation would at least yield us some base level of cooperation. At that point, if there are really

flagrant violators, we'll deal with them.

DOCTOR CAHILL: No data back, no more DNA from SEF.

CHAIRMAN LOWRANCE: Perhaps we should move on now to Doctor Mathews.

DOCTOR MATHEWS: For the past six months or so, I've been helping John Burris who is the Director of the Board on Basic Biology at the Academy, worked with the committee on mapping and sequencing of human genome, one member of which is Frank Ruddle.

Those of you who know anything about the Academy and the National Research Council know that I won't be able to really contribute anything substantively because we're obligated to maintain confidentiality until the report is released. But I can give you some idea of how the committee has operated and what our time frame is.

I can say that the committee has discussed in its four or five meetings virtually all of the details that Bob outlined in his discussion guidelines, including the issues of collaboration and information exchange and including ethics and ethical

implications of mapping and sequencing of human genome.

Of course, they've addressed the identical issues that have been raised here today on information handling and mapping and sequencing technology and the report will provide some technical background in those areas. And it will also probably address some issues related to benefits from mapping and sequencing a human genome.

But we're now working on the final, final, final draft and it will go out to the committee again for the penultimate final draft before it goes into review in August or so. And consequently, it probably won't be available until the end of September or October, something like that.

I don't know what else I can say. We have addressed, probably in just an oblique fashion, issues of collaboration, but they certainly won't be treated in any detail like you've discussed here today.

Other than that, I appreciate the opportunity to be here to listen to your discussions.

DOCTOR COOK-DEEGAN: John Gurson Stanley's in the back of the room, he just walked in, for those of you -- he's the other staff person.

CHAIRMAN LOWRANCE: Any questions that might be put to Doctor Mathews at this stage?

We have one more statement that I overlooked a minute ago in starting a section. I'm sorry. Mr. Dashiell from the Department of Defense has a presentation for us.

MR. DASHIELL: I won't call it a presentation, basically. It's probably a very short summary of a paper that I had published previously and I think Bob Deegan has copies of it that you can make available to committee members. It's basically a presentation I made some time ago, but things have not changed since this has happened.

In fact, you've had some interesting discussions this morning. I guess I feel a little bit like a fish out of water. I'm not a lawyer and boy, this morning it seems that you had to be a lawyer to understand what was actually going on. I'm obviously not an ethicist working for the Department

of Defense and I'm not sure that I'm even a principal in "technology transfer and MCTL," but I've been voted into that role, I guess.

I should say that DOD, from the technical side of the house, which is my side, has no programs in the area of mapping human genome. We're extremely interested in the outcomes of that, particularly as it may affect some of our programs in clinical investigations, clinical research, some of the work that's ongoing under our normal R&D program on what I'll just call infectious diseases research, because all these things are going to lead to the same objectives and that is better prophylaxis, better therapy and all those sorts of things.

We are extremely interested in the outcome, although as far as I know, we have nothing planned actually. We're more in the position of Dave Kingsbury. He has no focused efforts in that area.

With regard to the MCTL and the export controls --

CHAIRMAN LOWRANCE: MCTL means?

MR. DASHIELL: Military Critical Technology

List. Technology transfer and export control and all those sorts of things are actually administered by the Department of Commerce. We, the Department of Defense, Department of Energy, some of the intelligence communities cooperate with and provide review and consultation to the Department of Commerce on many of the specific areas.

To assist the Department of Commerce in the formulation of what we believe are critical areas of technology transfer, we do, in fact, prepare a document called the Military Critical Technology List, commonly known as the MCTL. It has a classified version and an unclassified version. The unclassified version usually gets wide distribution.

At this time, there are no controls in the area of biotechnology, in that sense, in the MCTL nor, as far as I know, and I'm a member of that group, we have none proposed. We are looking at some technology transfer of the kinds of technologies that may contribute to improvement in the military capabilities of potential adversaries in the general sense. Now, as biotechnology can fall into that trap

somewhere along the way, a specific item might or might not be included.

I guess kind of the bottom line is at this point in time, there is no interest nor intent on the part of the DOD to attempt to even control the kind of things that you've been discussing. You know, humanitarian, medical, agricultural items or applications. I think the kinds of controls that you may develop in your deliberation would certainly be adequate and would insure the kind of oversight that I think would be required in terms of technology transfer.

So, with that kind of a summary and if you need more details --

CHAIRMAN LOWRANCE: Thank you.

DOCTOR COOK-DEEGAN: I'll send a copy of that article to all the members of the panel.

CHAIRMAN LOWRANCE: Thank you.

I think at this point, first of all, I'd point out a small miracle, for which I'm grateful. We were supposed to conclude these presentations at 2:15. It is 2:13. I thank the presenters for being

so succinct and candid, in fact. Clearly, all of you are willing to say there are still some things to be worked out here. Again, we all look forward to OTA's doing that.

Let's take a moment to go back. You may have had some afterthoughts from the first presentations. Does anyone have any comments or general perspective now that we've heard these six different sets of comments?

DOCTOR WALTERS: I have a follow-up question for Doctor Kingsbury and that is why was your counsel so hesitant about putting conditions on grants? Is there something in the law or --

DOCTOR KINGSBURY: It was a question of being overly -- I don't remember all of the details, but it gets involved in who really has ownership. As you'll recall, and I'm sure you discussed in some detail here this morning, the government's policy about transferring the patent holding to the university or to the grantee, rather than having it return to the granting agency, which suggests then that the intellectual property is the property of the

institution which received support, in the case of a social science database, to require that that be put back into a repository.

I think that was the kind of question that had come up and it's a reasonable one. I think we simply have asserted that we want it this way and no one's challenged it. The lawyer ghetto over here can certainly discuss whether or not that is challengeable issue. I think that if someone objected, he might be a little bit on weak grounds, frankly. But that's never going to go outside of this room, I know.

DOCTOR COOK-DEEGAN: It's just a public transcript, that's all.

DOCTOR KINGSBURY: I think that's the issue fundamentally.

DOCTOR WALTERS: There may be an important distinction here and that is with human subjects research or recombinant DNA research where the rules govern the process of research, there's no hesitation by the federal government to say, "If you accept our money, you have to abide by these rules."

Here, it may be the product of the research rather than the process. There seems to be --

DOCTOR KINGSBURY: Well, look. I think that the fine point here is that the copyright of the book that comes from this social science research still remains with whoever writes the book. It's the raw data that we're really interested in.

So, I think that we're not asking for the book or the whatever to be in the public domain. We're simply saying the database, that is the collection of the data.

And I somewhat put this into the analogous situation of making cell cultures and microbial strains available. And if I could find a good way of putting an equivalent enforcement on the biological side of this, that we could really crank down on them, I would do the same thing.

This has come up as an issue at the National Science Foundation. I think all of us in the biological sciences at some point or another have dealt with people who are reluctant to send out strains or have been reluctant or have heard stories.

It's the classic case, "Yes, I will send you that strain as soon as my graduate student finishes writing her thesis." That may sometimes apply to graduate students yet conceived.

I don't think that's unusual. Perhaps I'm speaking too broadly, but I think all of us in the granting agencies would like to see less of that and make it more open.

CHAIRMAN LOWRANCE: Geoff Karny?

MR. KARNY: I think that's an extremely important area that OTA might focus on and that is what can be put into grants in the way of requiring dissemination of information. With regard to the ownership rights themselves, that has been pretty well decided by the Congress and by the regulations implementing the statutes. It's gone through a long history, starting with the OMB Circular A-124. In fact, there was even a predecessor to that and it's been embodied in the Federal Acquisition Regulation.

Those regs. are long and detailed. I don't recall exactly what it says about information itself. I think there is probably room there to condition

grant money on the disclosure of information. That may be an important distinction because the whole focus -- an important aspect of this whole discussion is getting the information out. People are mainly concerned about that and concerned that ownership rights might affect that.

To the extent that it can be segregated, I think it would be very useful to look at the two things separately and try to analyze how it could be segregated and what room there is for the federal agencies to place restrictions on the grant money, saying you have to disseminate the information in certain ways.

CHAIRMAN LOWRANCE: Doctor Kingsbury?

DOCTOR KINGSBURY: I don't want to make a long comment, but I think that it's worth focusing on it and bring up something that Frank Ruddle has certainly talked about before and that certainly is the view of some people that science is beginning to change and will continue to change in the near future.

Because of the expense of science and

because of the way we're now doing it, more larger centers of data generation are going to emerge, in biology as well as all across science. What we're going to see is more centers that are having extraordinarily sophisticated facilities that are going to generate the primary data vastly beyond what that center can process.

The role of many of us now as scientists may not be as data generators, but as data interpreters and data users and synthesizers. We now have to come to grips with this because if those centers that we're going to establish at enormous costs, do not put all of that data on-line immediately, then the system is going to break down. I think we're right on the beginning of seeing this happen and this is the critical factor.

So, I think it's to the interest of all of us to start to see that it's developed and discussed and --

CHAIRMAN LOWRANCE: Doctor Kirschstein.

DOCTOR KIRSCHSTEIN: I agree with Doctor Kingsbury, but I want to raise another point and that

is that you're talking about large centers. I think somebody has to speak for the protection of the small investigator in all this.

The small investigator whose livelihood depends on his or her next grant, and if the information about a very important new clone gets out too rapidly, that grant is gone. He's going to be in serious trouble. I have had a number of those people talk to me and they are deeply concerned about it.

CHAIRMAN LOWRANCE: George Cahill?

DOCTOR CAHILL: I just wanted to emphasize what David said. It's kind of speaking for our medical doctors over at Hughes. Big science is the name of the game and the scientist from now on isn't going to be so much RO-1 working with his graduate fellow but a manager. The more important to get the information generated by that big science available to the derivative scientist who will be using it, that could be one of the major problems.

DOCTOR KINGSBURY: Yes. I think Doctor Kirschstein is clearly expressing discomfort and I share her discomfort. But I think the point is this,

that we're only going to have so many -- there's only so many Purdues in the world. Mike Rossman can only be in one place at one time and have five of the most brilliant young structural biologists in the world with a dedicated super computer and there's only so many cyclotron beam lines. The fact is that those structural coordinates are going to be used by many of your RO-1s and R service people.

DOCTOR KIRSCHSTEIN: I'm not talking about that. I'm talking about certain other little things.

DOCTOR KINGSBURY: But the point is that those are the kinds of paradigms, I think, that are going to see development.

DOCTOR KIRSCHSTEIN: But we have to be careful about the balance.

DOCTOR STEPHENSON: One of the issues that comes up to me is this whole question of voucher specimens where people do research, report on it and then there is no way to verify the fact that it has, in fact, taken place.

DOCTOR KIRSCHSTEIN: That's another problem. Exactly.

DOCTOR STEPHENSON: We're seeing the issues with scientific publications where when someone does write back to find out is this organism, this modified whatever available, "No, it's not available. We threw it away. It's never been placed anyplace." These are issues not only for the granting agencies, but for the scientific journals that are not currently being addressed very efficiently.

CHAIRMAN LOWRANCE: Did you say that ATCC is offering to --

DOCTOR STEPHENSON: Another problem is the cavalier way in which a lot of resource programs are developed in the government, with no adequate thought or preparation made to the ultimate disposition of the material. That is a long-term situation. I thought I'd get that in as a --

DOCTOR KINGSBURY: He's referring in part to the fact that one day about two and a half or three years ago, I shipped to him four huge, giant liquid nitrogen containers with an incredible collection of tumor cells in them, many of which were not adequately cataloged.

DOCTOR STEPHENSON: Well, we just, last week, transferred Esther Letterberg's E. coli collection and the ultimate disposition of that still remains to be decided as to what's going to be done with it. Barbara Bachman isn't going to live forever or forever be at work and something's going to happen there. We've already ready taken care of Tracy Sanborn's paramecium collection on an emergency basis with no help from anybody.

These are issues that are really concerning not only me but the world level. We have established the Endangered Collections Committee at the World Federation of Culture Collections just to deal with these issues.

Here's all this stuff. You wouldn't think of trashing a library, but nobody thinks too much about trashing a collection which, in essence, is a library of DNA.

DOCTOR KIRSCHSTEIN: I think we have. We just don't know where to find the money to not do it. That's the trouble.

CHAIRMAN LOWRANCE: It sounds to me the

question of repositories in the broader sense would be a topic for yet another National Academy of Sciences review that cuts across all of the funding sources and the private sponsors, the university centers and so on. It is an infrastructure problem. Therefore, it's kind of nobody's problem. I wonder whether that could be different mechanisms, but it seems to me the Academy might be urged to think about that.

DOCTOR KINGSBURY: The Genetic Society, with Dan Lindsley as chair, has had an active committee working on this and has come out with a preliminary statement. We've worked together with them as one of the major supporters of some of these centers. In fact, I shared some of Bob's concerns. We've stepped in, in some cases, and kept things alive.

CHAIRMAN LOWRANCE: One of our tasks here is to cut very broadly across these issues. One of the things we haven't talked about, and maybe there are no issues regarding collaboration, is that of computer programs, mathematics, analytical techniques

and other related data analysis and integration methods. Are there any questions of collaboration or proprietariness and so on that need to be raised regarding software and not so soft information handling techniques? Maybe the answer is no, but while we were fishing, I thought I'd fish in that direction too.

DOCTOR KINGSBURY: I think there are policies in place in most of the agencies that deal with that. I may be wrong. We developed that some time ago and I think DOD has an identical policy.

CHAIRMAN LOWRANCE: Any other comments on that?

LeRoy Walters.

DOCTOR WALTERS: There's an issue that is in the discussion doc. guide that hasn't come up. I would love to hear comments from the members of the group here now on this issue.

On page 2 of our discussion document, about midway down the page, Bob Cook-Deegan raised the question, "At issue here are how priorities shall be determined." For example, which chromosomal regions

will be mapped or sequenced first?"

I wonder whether any of you have thoughts about a good method for coordinating that kind of decision making.

CHAIRMAN LOWRANCE: Could any of you point the finger at others?

DOCTOR KIRSCHSTEIN: That's what all our discussions have been about and that's what hopefully this committee, which is a subset of the Domestic Policy Council Working Group on Biotechnology, will try to do. But it isn't easy. It isn't easy because scientists have trouble with it. But I think it's more important that bureaucrats have trouble with it too. Each group wants to protect its own interests, very frankly. That's not very healthy.

DOCTOR CAHILL: The lingo is, the gossip is 16 is Los Alamos, 19's Livermore, 21 is Cantor and X is Gilbert. Is that correct?

MR. SMITH: Well, we are funding the first three. We're certainly not funding all the rest. There are many other efforts. There are a number of people working on various aspects of chromosome 21.

think that completion of any of these is --

DOCTOR CAHILL: I mean a systematic approach to at least the three, 16, 19 and 21.

MR. SMITH: Those efforts are underway, yes.

CHAIRMAN LOWRANCE: Sort of like mining stakes? I mean you drive a stake in the ground and say, "This is my chromosome." Is that about what it is at the moment?

MR. SMITH: Well, I think in the end all the chromosomes are there for a reason and --

DOCTOR COOK-DEEGAN: Except Y.

MR. SMITH: They'll all turn out to be important.

DOCTOR WALTERS: There is an effort that went on at the Institute of Medicine in a very different area and that was on vaccine development, to try to develop a systematic approach to the question of which vaccines ought to be developed first. It had to do in part with disease burden and in part with research opportunities, but I wonder if there would be any way to try to transfer that

decision making framework from infectious disease to the genome areas.

DOCTOR KIRSCHSTEIN: First of all, that effort came about a good 20 years after the vast majority of the vaccines were all developed hundreds of years before. So, what they're trying to do is prioritize. I worked in the vaccine field for a very long time. Prioritize what's left, other than something new that came along that they didn't even think was going to come. I was on that committee when they did it. So, we're starting at very different bases along the way.

CHAIRMAN LOWRANCE: Doctor Kingsbury?

DOCTOR KINGSBURY: Well, I think it's worth reiterating in response to that question, that there are two kinds of activities going on and there probably always will be. That is, the kind of focal effort that identified chromosomes that they were talking about, then there's the local sequencing and the local mapping that goes on because of people's intense interest in a problem that revolves around that segment of the genome.

That's what drives it, is the quality of the science and the kinds of scientific questions that can be asked and answered and addressed and I think it will always be that way. Our peer and merit review systems are revolving around the quality of the science. For the most part, that will be the driving force.

CHAIRMAN LOWRANCE: I think we're doing quite well. Could we, at this point, consider that the formal part of the presentations is concluded. But we invite you to stay at the table and stay with the discussion until we conclude around 4:00, because you have very valuable perspectives. On the other hand, if you have to go off and put money into this budget, I suppose you can be excused.

Patricia Hoben, you had a concern that you raised with Bob a few minutes ago. I wonder whether you'd like to raise that with the group, just to broaden the discussion.

DOCTOR HOBEN: Well, just to go back briefly to the copyright ability, because it's an important question, we've been asked to address it.

I don't think we've addressed it. I think one of the problems is to give a little bit of a better scientific background maybe to some of the attorneys to pose the question differently.

My understanding is that as an author, the United States is not patentable, the land. It's not copyrightable. But I can draw a map of that, correct, and copyright that?

If that's true, that's the analogy I think that Walter Gilbert's company is using. He's not trying to patent the human genome or a single clone of a fragment of chromosomes, but the order of a map which he will create by cutting at whatever sites he so deems as correct, putting them into a plasma carrier vector and then ordering them. Then on a computer printout or in whatever way he wants to do it by computer, come up with a pictorial representation of a map which he authors and creates.

Could that not be copyrightable? And if so, the key question for us to address for Congress is, how would that affect the public domain issue.

CHAIRMAN LOWRANCE: You're looking at the

lawyers across the way. Are there any responses?

MR. GOULD: I think what you're protecting is the representation of the way it's organized and shown, not the information itself.

DOCTOR HOBEN: Right.

MR. GOULD: The other person could not duplicate the representation, but is free to use the information that's contained in it.

DOCTOR CAHILL: All that's important is the sequence of GCAT.

MR. GOULD: You don't protect the sequence by the map. You're protecting the way it's organized and shown. That's the authorship, that's the contribution.

DOCTOR CAHILL: I don't think you understand. The ultimate thing is going to be on Chromosome 21, about 100,000 GCATs lined up.

MR. GOULD: Yes, but the sequence itself, the information of the sequence, G-C-A-C-T, is not protected by copyright.

DOCTOR HOBEN: That's not what I'm arguing. What I'm arguing is the physical map of an ordered

set of clones.

MR. KARNY: That probably is copyrightable.

DOCTOR HOBEN: The question is, by having that copyrighted, are you going to limit accessibility to that information?

MR. GOULD: You can't protect the information if you make a directory of addresses, telephone numbers and so on. You can do the representation the way it's physically shown, but not the information that's contained in it because that is not the basic copyright.

DOCTOR RUDDLE: Is it true then if a second party goes back and uses the same information and derives another map from it, that that would be equally copyrightable?

MR. GOULD: Absolutely, and he came make this exact same map, identical map independently. And he's free to do that. But he cannot copy your representation. You cannot physically go out and publish that map because if there's any copyrightable organization in it, the person who's the copyright proprietor can prevent other people from publishing.

That's the key feature of copyright protection, publishing the map. It has nothing to do with use, it's publication.

DOCTOR CAHILL: I don't think you understand. Can I patent the fact that the liver is beneath the lungs?

MR. GOULD: No.

DOCTOR CAHILL: Or copyright is what I meant to say.

MR. GOULD: No.

DOCTOR CAHILL: That's exactly what we're doing here. It's an anatomical linear array --

MR. GOULD: You can draw it and you can copyright your representation.

DOCTOR CAHILL: -- whether you draw it on yellow or green ink.

MR. GOULD: That's exactly right.

DOCTOR CAHILL: But that doesn't mean a damn of -- what's important is the anatomical relationship --

MR. GOULD: But that exists. You can't copyright.

DOCTOR CAHILL: Therefore, Gilbert can't copy the human genome.

MR. GOULD: He can copy his representation of the genome, but not the information --

DOCTOR CAHILL: So, it's useless, in other words.

DOCTOR KIRSCHSTEIN: I don't think it is, George, and that's the question. It is useful and he can probably get money for it because it saves everybody else an enormous amount of time and reproduction and spending of money to derive the same information. So, until somebody challenges him on that, he's going to make money on it. That's the issue that the rest of us --

MR. GOULD: But not through the copyright because the copyright protects you --

DOCTOR KIRSCHSTEIN: No, he's going to sell the representation, sell the books.

MR. GOULD: He can sell it once and anybody that wants that information out there can use it any way you want. It would be better to have it as a trade secret. That makes more sense.

DOCTOR KIRSCHSTEIN: That's the important piece of it.

DOCTOR RUDDLE: The way I look at it is that here we have a map of the human gene cell which we've put together from various sources. We can copyright this book. We could even sell this book if we wanted to. We're not selling it, we're giving it away. But if we wanted to, we could sell it.

Someone else could not come and copy this book and also sell it, but they could go back and get the original data if they wanted to take the time and effort to do it.

DOCTOR KIRSCHSTEIN: That's right.

MR. GOULD: Or use your book and use the data that's in it.

MR. KARNY: Take it into a lab and use it however they want.

MR. GOULD: That's right.

DOCTOR MATHEWS: But if it appears similar to their book, there's the implication of plagiarism.

MR. GOULD: He could prevent me from copying the book and publishing the book. That's

what the copyright protects.

CHAIRMAN LOWRANCE: But not using the information in some other way.

MR. GOULD: Not using the information.

DOCTOR KINGSBURY: Even if it looks alike, because all copyrighted maps of the state of Washington will look alike.

MR. GOULD: Will look alike. But they may not be all blue or yellow or red.

DOCTOR KIRSCHSTEIN: He can charge for the information.

MR. GOULD: But that is a trade secret right. No, no, no, he cannot do that. If he publishes it and distributes it, he can only prevent other people from republishing the book, copying the book. He cannot prevent you from using the information.

DOCTOR KIRSCHSTEIN: He can charge for the book.

MR. GOULD: That's right.

DOCTOR KIRSCHSTEIN: Well, that's what I'm saying.

MR. GOULD: And once you charge him for the book, it's out. You're free to use it whatever way you want.

CHAIRMAN LOWRANCE: This is a useful analogy, Patricia, and I hope Susan Rosenfeld, you will throw as much light as possible on this as the summer goes on.

Mr. Karny?

MR. KARNY: I think the copyright issue is a good one to look at in greater detail. I think one impression I personally do not want to leave is it's a non-issue. I don't think it's a non-issue. I think it will probably turn out to be not very troublesome, but it really seems to me it does require some very good analysis in the context of a number of good examples before we're comfortable.

I'm saying that it's really not going to be a problem. I think it's worth going through the analysis, but I think we'll find that it's not going to be a major problem. At least we'll have the comfort of knowing that we worked through it and we have a basis for that conclusion.

DOCTOR RUDDLE: I think the key issue that needs to be resolved is whether the first party does the analysis of achieving a sequence, whether that precludes a second party from doing the same thing.

MR. KARNY: Probably not.

MR. GOULD: Not by copyright. And you don't get copyright protection until you publish with notice. That's the key of that. You must publish it and make it available with your notice of your copyright. Then your protection is, again, you prevent other parties from copying that publication and republishing it. That is the nature of a copyright.

CHAIRMAN LOWRANCE: Bob Cook-Deegan is going to raise another issue for us.

DOCTOR COOK-DEEGAN: One thing I wanted to raise though is to focus specifically on the issue that David raised in connection with the--essentially, I think one of the first things that would result from the ongoing efforts that have already started would be a set of DNA clones that would be stored someplace.

I'd be interested in any experience -- that was raised an issue, but we haven't really discussed it. Any issues that have already come up in connection with existing clone repositories, what have been the sticking points and what are the access rules in connection with that? Are they all the same or are there different rules for different kinds of materials like probes and clones and vectors and stuff like that?

DOCTOR KINGSBURY: Ours are all pretty much the same and the sticking point is that we never give Barbara Bachman enough money to ship everything out. That is always the issue with any of these. At least our experience is we starve them.

We've discussed this a little bit before in this context. I'll just mention it again. The magnitude of the problem is one that's mind boggling. The E. coli strain collection right now has less than 10,000 strains in the inventory. They're all very detailed. She knows every allele and every marker and what have you, but there's under 10,000.

You're talking here, if we had the full

cosmid collection, we're going to approach 100,000 perhaps or more.

DOCTOR COOK-DEEGAN: Well, in fact, Brickmeyer's projection for us was 350,000.

DOCTOR KINGSBURY: Yes. And if you think of the expense and time and effort that it takes to do less than 10,000, this is a big, big job. It's unbelievable. You've got problems with this collection, with the cosmid collection, that we've never dreamt of with the E. coli collection because E. coli -- you know, there's a few funny things that happen, but generally they're stable. They're not going to have repeated sequences that they're not going to like and spit out. So, if you get the clone today, it's going to have 15 repetitions and you get it next year, it's only going to have ten.

DOCTOR RUDDLE: It may turn out that these kind of repositories will actually be databases. So, all of the cosmids will be characterized in terms of a sequence and then any laboratory that wants it or needs it will find it easier to generate the oligo and fish out the cosmids themselves. So, it may not

be necessary to have a wholesale Sears and Roebuck operation for cloning and sending out these things.

DOCTOR KINGSBURY: That's a good point because it may be the only realistic way of doing it.

CHAIRMAN LOWRANCE: I wonder if Doctor Alford, as one from the private sector who's going to be drawing on some of these kinds of materials, whether you have perspective on the kinds of things that have been coming up here, repositories --

DOCTOR ALFORD: There's really no set depository right now that we can see that offers everyone what their needs are. One must remember from this morning's discussion, it's not just maybe the private sector that maybe some people feel that were not so willing. We are willing with a collaboration.

There's also the academic centers. There's a lot of probes out there in the academic centers that are involved with the same kind of research that we're involved with and we really can't access their probes today. There's not any kind of agreement the two of us can come to where I can use their probe.

So, we would love to be able to and we will participate in a repository.

But again, I have to restate that we would like to participate in a repository. We will because that's the only way that this problem will be solved. But somehow, we're going to have to be able to protect our rights, our commercial rights. We're not sure how that can be accomplished right now and we hope that we'll be able to solve that.

My company specifically believes that there's no way that we could accomplish this genomic project without having some kind of central repository. There has to be one. Collaborative will have to participate, will have to put their probes and there other pieces in there. But I don't know how that can be really set up.

CHAIRMAN LOWRANCE: Doctor Stephenson?

DOCTOR STEPHENSON: We have participated with co-data in the development of a hybridoma data bank where the data about hybridomas is collected, edited and made available on-line and in hard copy as necessary. Something of that type could be done, in

which case then you could list as to whether the actual material itself was available or only information was available about it.

That data bank, in essence, serves as an honest broker between interested parties but does not get involved in the transaction of setting up collaborations or licensing or whatever. It just says, "Here it is. This is what we know about it. If you want it, go talk to the people who have it." I think something like that could work in a case like this.

DOCTOR ALFORD: It could. In the SEF database that was alluded to before, we have given a lot of information to the SEF database because we get information. But I think, if you look at specific examples, unfortunately, I want some of those actual probes. I want more than just the database information. If I'm researching a specific genetic disease and I find out -- the rumor mill is just tremendous in this business -- that someone has a probe, I'd love to be able to call him, as I hope he'd be able to call me, and send it to me. I want

to use that, the probe itself, not just the information.

Like we talked about this morning, it's a combination of both. It's the information and it's the material. They're two separate things. But I agree with you. That would be tremendous.

DOCTOR STEPHENSON: That is a way to publicize the availability of a probe and then set up some kind of these recognized mechanism --

DOCTOR ALFORD: And then you know who has it.

DOCTOR STEPHENSON: You know who has it and also there could be some international convention on how to write up a very simple contract or whatever between the parties that they would respect each other's rights and make the thing into a routinized procedure rather than something where each time you had to get a lawyer and approach the thing as if it were a brand new product.

DOCTOR ALFORD: Yes. We really don't want to have to do that. No one wants to do that. If it could be a simple, more routine setup, it should

work, form kind of setup. Hopefully that would help in the future.

DOCTOR RUDDLE: I think it's a good idea. The idea then would be that some commercial groups or groups that hold probes would map their position and then put this into a database. They may or may not be available. At least people would know about them.

DOCTOR ALFORD: Or maybe they could be available, but maybe they could be restricted. I would hope that you won't start a company after I give you my probes for that genetic disease. But if we're both very excited about an F or something, then it would be nice to be able to share our information so that we could further the science of that disease.

DOCTOR STEPHENSON: Yes. But I think the thing is that your company or any company that's doing this kind of work doesn't want to put all of their probe material into the public domain.

The information is available as to the existence of those probes. Then you can follow it through one-on-one negotiations.

DOCTOR ALFORD: I can't really put all my

probes in because I don't think I'd want to face my investors at the next board meeting. But I'd like to put that information in so that we could all use it. Yes, I agree.

DOCTOR RUDDLE: Do you think your investors would object to that?

DOCTOR ALFORD: No, I don't think at all because it would be furthering the return on their investment. That's what they're looking for. But they don't want me to give my property rights away.

DOCTOR RUDDLE: Well, we'd be happy to take your data any time.

DOCTOR ALFORD: Thank you very much. There's a few probes that I'd like right now.

DOCTOR COOK-DEEGAN: I wanted to pursue this model for just a second and I wanted to find out what the -- using this monoclonal database as an example, it sounds like that model provides a database clearinghouse function without direct linkage to a repository. And using that model again for these physical map overlapping clones that might be at Livermore, might be at Los Alamos, might be at

Columbia, might be at Washington University.

Was that the intent of this monoclonal antibody thing? That essentially means that the repositories would be at the original institutions, is that right?

DOCTOR STEPHENSON: Well, it varies. We have, for example, a hybridoma bank of cell lines, all of which are in that database, but by no means are the two continuous -- or whatever you call it.

DOCTOR COOK-DEEGAN: You're saying not everything that's in the database is there?

DOCTOR STEPHENSON: Not everything that's in the database is in the bank by any means and some of these things are scattered all over the world. The thing that the database does is give you the physical and immunochemical attributes of the generated monoclonals, the antigen and what's known about it that generated the thing, all the nitty-gritty information. Then it also says, is this a patented material, is it available for distribution and/or license, the name and the address of the investigator and who you may right for more

information.

So, as I say, it's basically an honest broker service. You can take the database, you can cut it, slice it, reassemble it and do all kinds of things in terms of making tables of similar things on the basis of different properties, et cetera, so that you can play with it as a database in real time with generating information from the database and evaluating or interpreting. But you can also use it as an order system to go get the stuff that you want.

So, I think it has a lot of virtues because you don't then tie up all of the thing to having all the material in one repository. You can have multiple repositories all over the world.

CHAIRMAN LOWRANCE: Doctor Kingsbury?

DOCTOR KINGSBURY: There's one thing about hybridomas though that are different and that is the policy of many places that you don't care about the hybridoma. It's the antibody that you want. That's one of the reasons why people are handling those differently. Many people will not provide you with hybridomas, but they'll give you as much antibody as

you want.

So, that's quite a bit different. Here, with these cosmids, it's quite different. There you need the cosmid. It's not a perfect analogy. It's not bad, but it's not perfect.

CHAIRMAN LOWRANCE: Doctor Ruddle?

DOCTOR RUDDLE: I was just going to point out that the database, the gene mapping library database does provide information for finding probes. So all the probes are listed here. There's at least an attempt to identify where they can be obtained and an address system for their access.

CHAIRMAN LOWRANCE: Other comments on this general point? Yes?

DOCTOR COZZENS: My imagination is caught by this idea of a simple agreement that people could sign that would make it easier for them to share probes than it apparently now is. Something that would by symmetrical, that everyone in the community would have. And whether you were in a commercial organization or in a university, when someone comes to you for your probe, you just say, "Fine, I'll send

you the probe as soon as I get this signed consent form back on what you're going to do with my probe."

Now, what would be in that agreement if it were written up in a one paged form? What would the whole community -- ask everybody else in the community then to do with their probes. Is there, in fact, such a set of kind of principles that there'd be consensus on?

DOCTOR RUDDLE: Depending on the players, I think, on the individuals who are making the agreement. If I write for a probe to another researcher, they may say, "Yes, you're free to use it for academic purposes, but we would like to know who you sent it to or we restrict your ability to send it to another party or to use it commercial purposes."

The relationship between an academic person and the company might be a little different. A company might want to have a more circumscribed use of the property, but it could be worked out.

DOCTOR ALFORD: But the comments you just said, it sounds like we'd ask, to use it for your research, not to use it commercially and probably we

would ask you maybe one other thing, don't give it to another party. If someone wants it, they can contact us and I'd be glad to have that letter agreement with them.

So, fundamentally, I think we're asking for the same thing because what we put into our simple agreements, if you will, are the same things that are put into the agreements we sign to get probes from academic institutions. They really look identical because it's a simply one page agreement.

CHAIRMAN LOWRANCE: Other comments on this point?

I wonder if we could turn then to the international questions again, something we haven't really taken a big bite at today. We're coming near the end of the agenda, up to the point of asking what OTA should do next, but I think we ought to spend a minute on international, just to see whether there are dimensions that are somehow different from the things that have been coming up all day because they are transborder.

Any aspects that anyone thinks of that have

to do with barriers to collaboration? We heard some discussion this morning of the patent questions.

Doctor Stephenson?

DOCTOR STEPHENSON: There are three inter-union, interdisciplinary committees currently that I could conceive might have interest in this general area and we should be informed of your concerns and invited to give feedback. That would be Co-gene, Co-data and Co-biotech, which is a new coordinating committee from just a few months ago.

But these three -- Co-data, for example, is the agency that is now supporting the hybridoma data banks. Also supporting the development of the microbial strain data network on an international basis. They have gotten away from totally physical and chemical constants now to begin to look at some of the biological standardization issues. I think they should be encouraged to continue. This is a good example of one of the things that they should be informed and participate in.

CHAIRMAN LOWRANCE: Other comments on the international dimensions --

DOCTOR CAHILL: Co-data is what, the National Bureau of Standards? Who funds them?

DOCTOR STEPHENSON: They are funded internationally. They're an interdisciplinary committee with representation from the international unions of immunology, microbiological societies. It's out of the ICSU family of Council of Scientific Unions.

DOCTOR KIRSCHSTEIN: A lot of their funding comes from us. They've been funded a little bit here, a little bit there, a little bit everywhere.

DOCTOR STEPHENSON: Yes, it's international.

CHAIRMAN LOWRANCE: Doctor Smith?

DOCTOR SMITH: I just wanted to make a general point. It seems to me that a lot of the discussion this afternoon is on what one might call project design. How does one put together an architecture of a project where you've got clean interfaces where you insure that there's not a replication of effort and you are saving money by not doing things in the most expensive ways because

people are sharing techniques and showing that the data is considered very early in the planning phase, what you're going to do with the data.

This, it seems to me, is one of the major historical lessons from studies of big sciences. Often, people do not think of the overall project architecture in the beginning. They indulge in what one might call an ad hoc crusade and they kind of stumble along. Whereas if you've got your end products in mind and the overall architecture in mind, you've worked that out clearly, which will improve the international cooperation, for example. Then you end up with a much better project.

CHAIRMAN LOWRANCE: Mr. Karny?

MR. KARNY: I throw this issue out with some trepidation, but it might be interesting to see the reaction and might be interesting also for OTA to give some thought to it. That is, if we're talking about some giant centro-project here and maybe is that is not knowing how this whole project is going to evolve on the federal level or series of centers, as I understand it, it could go that way and we could

be seeing an incredible amount of federal money being put into this, i.e. taxpayers money.

I'm wondering if it makes sense to try to, from these centers, control to some extent the information coming out, to the extent of at least trying to recover costs, if not from U.S., certainly from other entities abroad. In other words, why should we spend $5 billion of the taxpayers money to create a database that the Japanese will use to come back and sell products in our country.

That's very much of an oversimplification in many respects, and I certainly don't mean it to be inflammatory for the Japanese, but there is this idea of taxpayers' money and the work being done here and somebody else perhaps getting the long-term economic benefit. I realize there's a lot of negative implications there, but perhaps it's something to think about and consider.

CHAIRMAN LOWRANCE: Any comments on that?

MR. GOULD: Maybe we focused the wrong way. Maybe we should be inviting other countries to collaborate with us. I don't think this program is

essentially American necessarily in nature. It seems to be an international problem. It might be approached by it as an international cooperative technology. Therefore, everybody contributes and people will then have access to it.

CHAIRMAN LOWRANCE: My understanding is that there's a lot of movement in that direction.

Bob Cook-Deegan has a point he'd like to rise.

DOCTOR COOK-DEEGAN: It's perhaps one of the reasons we're having such a hard time getting a discussion about the international issues, which I think are particularly intractable, frankly.

DOCTOR KIRSCHSTEIN: Particularly what?

DOCTOR COOK-DEEGAN: Intractable. They're very difficult for us to deal with analytically. If you read my interim memo of May 7th, I'm flopping left and right and flailing quite flagrantly in that section of my report. It's because it's a very difficult thing to deal with.

I just wanted to see if I could generate a little bit of discussion that would be useful to us

in thinking through these issues and I just want to take one more stab at it before abandon this.

Yesterday I was talking with two folks at one of the big centers of molecular biology in the United States and I went from one laboratory in the morning and his comments on the international section that I'd written were that he thought it was totally naive and pie in the sky and there was no potential for international collaboration on two basis.

One is the issue that you raised, Geoff, which is essentially if you're putting money into technologies, public monies into technologies, it's going to be very hard for the governments to say, "Let's share this." And on the other end saying that past agreements on databases, where it seems there is agreement that the information should be internationally available, it's nonetheless sometimes difficult to set that up.

Now, EMBL and GenBank may be an example of where there's a working relationship that has persisted for several years. But he still thinks that it's almost impossible, when you're talking

about things that involve DNA repositories and things like that.

Then I go to another person three hours later, same institution, also a bright person who says, "Gosh, international collaboration should be very easy because everybody wants to do it." I would like a sense of where those two perceptions are coming from because it's very fuzzy in my own mind and I have to write about this.

DOCTOR KIRSCHSTEIN: Well, let me talk about EMBL and GenBank for a minute because it's more than EMBL and GenBank now. The two groups were basically set up separately but knew right from the beginning, because of the way science is done and the way people talk to each other that they were doing a little bit of the same thing. So, right from the beginning, the person at EMBL was invited to all the implementation plans for GenBank and the GenBank people were invited to what was going on in EMBL.

It's been more of a one way street from EMBL here than backwards, mainly because, just as in everything else, the federal government doesn't

provide enough money for the United States workers to go abroad to consult with the people in Heidelburg. However, we did manage to do that last February and out of it came considerable collaboration and the Japanese were there too.

And now, as a result, primarily spearheaded by the Director General of EMBL and Doctor Weingarden and myself, but the Japanese will cooperate, we will have an international advisory council to the whole nucleic acid sequence data bank which will probably be established by September or October. It will have three people from EMBL, three people representing GenBank and two from the Japanese. The Japanese is more than the Japanese, because they have now agreed to try to collect data from the entire series of countries in the Pacific.

CHAIRMAN LOWRANCE: Any other illumination for Bob?

MR. KARNY: Does that help you?

CHAIRMAN LOWRANCE: That's not going to stop him from flopping and flailing.

DOCTOR COOK-DEEGAN: I'll tell you, I think

there is -- in all the people that I've talked to, there is consensus, databases, that the scientific information should be freely available. As soon as it's available in one place, it should be available to everyone.

The sticking point seems to be in that transition from science to technology, which is also where you have the tough decisions about deciding which chromosome to do and which -- as there's a transition from a scientific project to a technical project, where everybody kind of understands how it's going to go, but the data is, nonetheless, going to be valuable. It becomes harder to set priorities and it also becomes harder to share the probes and the clones and the hardware and the information that went into the hardware.

That's the area where I'm having the biggest struggle. I don't even know how to attack that, other than to say it's a quagmire.

DOCTOR STEPHENSON: It seems to me that if people are interested in it and want to do that, they will find some way to either build the instruments,

buy them, import them or whatever and you don't have to worry about that unless Dashiell decides all of a sudden it's on the Militarily Critical Technologies List and we can't export them if we happen to be making those instruments. God help us if some other countries decide to do the same in reverse because we're quite dependent upon other countries for some of that instrumentation ourselves.

One of the problems that we have with shipment of cell lines back and forth has to do with culture media coming from animal sources that the Department of Agriculture controls. But I don't think you're going to have that in these materials, so that the international transfer of the biological materials per se should not have any regulations or restrictions on it as far as I'm aware. And so there should be a free interchange of that. The material is not infectious, it's not containing exotic agents or whatever.

So, I think it boils down to just a simple question of is there a will to do this kind of work and if there is a tendency to want to share the

information, it will be shared. I don't see that there are any constraints or problems that I can define today that would inhibit this process. The only thing is the desire of people to get the job done.

CHAIRMAN LOWRANCE: Any other comments for Bob?

DOCTOR CAHILL: I'm just concerned that if we focus on trying to set the pathway up as an international effort that we will delay decisions of the United States in proceeding with this. I'm very glad that Boeing Aircraft did not join the comet manufacturers when they introduced the first commercial jet and that we set our own priorities and our own pathway for executing that technology development. I'd like to see the same thing done here, indicating a willingness to cooperate at the international level, but setting U.S. national priorities.

DOCTOR COOK-DEEGAN: So that model would really be cooperated at the back end of the data or out and not worry too much about the front end and

priority setting and things like that?

DOCTOR CAHILL: I want to see the project underway.

DOCTOR SMITH: What would be the reasons for international -- are there compelling reasons?

DOCTOR COOK-DEEGAN: The rationales that have been proffered and the language for this is quite explicit in a rather vague proposal by the Japanese, for example, in the human frontier science project. This sort of thing could fall under that. The rationale provided in that language is that the value of this is pervasively international. That is, the book of man should be available to everybody. Therefore, it follows that it should be international collaboration.

That's rather vague and that tells you that you do need to collaborate at the back end if you've got the data. It doesn't tell you much more than what it means, but there is an effort to try to gather -- to get feedback on whether it makes any sense to try to do collaboration at the front end, that is in designing the project. I know in physics,

there have been attempts to do that. The Bureau of Oceanography space telescope is perhaps an example of that.

DOCTOR SMITH: That was because of direction from the Congress. This isn't usually what happens. There's no choice about it anyway. It's kind of Congressional fiat, "You will collaborate because that makes it cheaper for us."

DOCTOR COOK-DEEGAN: Could you give us a judgment based on your knowledge of what's happened in physics about whether that sort of thing tends to work? When Congress says it's going to be an international effort and to make sure you set that up in advance, does that work or does that not work?

DOCTOR SMITH: There are some very successful international projects, particularly with scientific spacecraft that I can think of. But often, the argument that one gets from American scientists is that, well, the Europeans have made a commitment putting, say, 15 percent of the development costs, but that's a selling figure.

So, the actual cost of the project is much

higher than that. So the Europeans end up getting maybe 15 percent of the observing time for putting five percent of the money, which is often inequitable. So there's often a resistance from U.S. scientists for European collaboration in that respect.

Often it's seen purely as a measure taken by the Congress to save money on the project up front. In terms of the kind of bringing a community on board to a project, it often makes things harder, although easier to sell within the Congress.

CHAIRMAN LOWRANCE: Doctor Kingsbury?

DOCTOR KINGSBURY: Well, I'd like to, in a sense, reiterate what Tom was saying. Another one of these international experiences that may work as a model and that's the ocean drilling program that NSF runs. We put together a platform and we funded a platform and it pushed off and it's out trying to drain the ocean and we get international cooperation, in the sense that it is a unique platform. There is no other platform like it.

We have gone to European countries, we've

gone to Japan, we've gone to countries that we won't name and talked about, "Yes, we have platform time and you can decide where we're going to drill a hole, if you put in the money. We want your collaboration." The data is shared among everybody. But we built the platform and we decided where the first holes were going to be drilled and we went out and started drilling.

We want as much international cooperation as possible, but it was driven by the scientific interest.

DOCTOR COOK-DEEGAN: So that model, essentially we say, "We're doing this and then you can join after we've written the rules."

DOCTOR KINGSBURY: Right. "If you want to get in on this, hey, that's wonderful, but we're going to go out and drill holes."

CHAIRMAN LOWRANCE: LeRoy Walters?

DOCTOR WALTERS: What is the scope of international cooperation that you're thinking of, Bob? One thinks immediately of Japan and Western Europe, but are you also thinking of possible

collaboration with political adversaries?

DOCTOR COOK-DEEGAN: I have nothing in mind at all. I have no idea what I'm talking about.

DOCTOR WALTERS: Well, let me make the question more pointed. What would be the pros and cons of a proposal to collaborate with the Soviet Union on the human genome mapping project?

DOCTOR COOK-DEEGAN: I think pros would be whether there could be cost sharing. The cons would be whether there's international transfer of technology that might be militarily useful or even economically useful in the case of the Soviet Union, the difficulties of doing it and whether the scientific community in genetics in the Soviet Union would be sufficiently strong to merit that sort of a collaboration. That's a strong con, I would suspect. In this particular initiative, they don't have a great expertise in genetics.

Nonetheless, there might be strong political rationale for saying this is a good opportunity to show good will and international peacemaking.

DOCTOR STEPHENSON: If you took the same thing and applied it to the Japanese situation, there is a group in Japan. They do have a stated commitment. I believe they've even identified two chromosomes that they have ambitions for mapping. They do have a consortium of government, academia and industry that is providing the instrumentation and some of the financing to get on with the job.

So, in that case, you're talking about something that is there that is existent and where one could, in fact, divide up turf and put some substance to a collaborative process.

CHAIRMAN LOWRANCE: Other comments on the international aspects? Yes?

DOCTOR CHILDRESS: I think one reason we're having difficulty in sharpening this a bit is it does seem to be largely a practical question. It may or may not be advantageous, depending on the state of scientific development, whether they can really contribute on this particular matter. But also, it seems to be on the cost factor. So, it really is a practical matter.

I guess what I want to throw back in your lap now, or your side of the court, is what kinds of problems would be raised of the sort we've already dealt with today when we put it on an international level? How significantly does that change things or do we simply work with the same kinds of problems we were dealing with earlier today, possibly the kind of agreements that will permit the sharing of information, appropriate protection of proprietary interest and so forth.

DOCTOR COOK-DEEGAN: I was kind of hoping it would be the receptacle of information. To answer that, I think in terms of databases and things like that, I think there are mechanisms for handling that sort of thing and it's not a big logistical problem because you're talking about databases and there seems to be an international consensus that each government should be willing to spend some money to support that sort of thing.

In terms of trying to come up with practical solutions to collaborations, I haven't heard any concrete proposals floated, other than kind

of saying, "Let's do it the way we do other science. You find your stuff, we'll find our stuff and we'll talk to each other when it's done." There's nothing wrong with that model, it's just --

CHAIRMAN LOWRANCE: George Cahill?

DOCTOR CAHILL: It's been pointed out to me that the most interesting part is not the primary sequencing but the horizontal comparisons of the human genome and that's going to require a lot of ethnic racial population. With the Americans being a mixed population, it will be tremendous input looking for polymorphouses, preparing subsets around the world.

That's why there's a critical reason for the comparative biology of man to do this. I think some of us -- I'm not in it, but those that are in it place a very high priority to get this comparative information. That's why we have to bring these other countries in.

DOCTOR COOK-DEEGAN: Just to float one thing specifically on that point. David Weatherall of Oxford is doing a piece for OTA on looking at how

the third world countries might be able to use mapping sequence information. So we'll be addressing that at least a little bit in our report.

CHAIRMAN LOWRANCE: I wonder if we might turn now to talking about, before some final comments on it, what this panel urges OTA to do in the next couple of months. Any subprojects you'd like to see, that we'd like to see spun off and contracted? You might tell us of a few of the things that are going on, such as the one we just mentioned, that we should be aware of. Then we can add to that list.

DOCTOR COOK-DEEGAN: I'll just list the contracts, perhaps. What I'm mainly interested in is if people around the room have ideas of approaches for issues that were dealt with today that we may not have thought of.

Patricia arranged for a contract by Daniel Levlis and Doctor Howbran of Berkeley to make comparisons between other big science projects and this particular one. I think they'll be looking at cyclotrons and things like that, watching the historical evolution of physics projects and seeing

what lessons could be learned for this.

David Weatherall is looking at the third world applications of mapping sequence information.

Ted Freedman will be writing a contract for us on medical uses of mapping sequence information. He's a physician, molecular geneticist from U.C. San Diego who is one of the people who has thought about mapping and sequencing. In fact, he's doing it in his lab. I don't know how he's being supported.

Are there any other relevant contracts? There are ten or 15 contracts that we've got. I think those are the main ones that are relevant today.

DOCTOR COZZENS: Two international.

DOCTOR COOK-DEEGAN: Oh, there are two international contracts. Peter Neumark, who is European correspondent for Nature, is reviewing Western European policies, looking at the UK, France, Germany, the EEC arrangements and anything else he turns up, and Italy, which has something of a commitment in mapping and sequencing.

And Aki Yoshikawa from the Berkeley Round

Table International Economy is looking at policy setting, particularly within the Science and Technology Agency and the Ministry of International Trade and Industry in Japan and trying to find out how they're deciding what to do with their genome efforts, mapping and sequencing, most particularly in developing hardware. We're just trying to find out what's happening.

Any others that are relevant?

DOCTOR CASKEY: Bob, one you and I mentioned at lunch time, the applications of the map to diagnosis.

DOCTOR COOK-DEEGAN: Yes. Ted Freeman's picking that up to some extent specifically for mapping and sequencing. OTA has another large project that's about three-fourths done that's looking at issues of confidentiality, privacy of genetic information, looking specifically at human diagnostic and human genetic screening applications, which would include looking at diseases specifically and also looking at risks of developing atherosclerosis or cancer or something like that.

That's a very large project that Tony Holzman has been doing. That one will probably come out more or less the same time as this one, but it's a separate effort.

CHAIRMAN LOWRANCE: Any suggestions for OTA of other such subprojects that could be undertaken? Of course, there's the Bar Association's project.

DOCTOR COOK-DEEGAN: Yes.

Mark?

CHAIRMAN LOWRANCE: Would you identify yourself?

MR. PEARSON: Mark Pearson. I thought one of the interests extending the sequence information was to its potential utility in rational drug designs. So, it's a therapeutic aspect that goes beyond the diagnostics that's been mentioned before. Is that going to be contracted?

DOCTOR HOBEN: I'm writing about that. I'm not contracting it, but anything you want to send me.

CHAIRMAN LOWRANCE: Any others of this sort?

DOCTOR COOK-DEEGAN: Is there anything in

the repositories area? That's been discussed a lot today. Is there any way that we can gather -- sounds like that's a key issue, frankly. One of the bottom lines I'm getting from today is we need to find out about copyrights and patents, is kind of the threshold question. We also need to look at repository issues.

Sounds like DOE has -- I guess there's some sort of arrangement with DOE and DRR to kind of at least think about it. Is there anything that OTA needs to do?

DOCTOR KIRSCHSTEIN: I think it's an NIH problem as a whole, working with DOE, because we have a committee to look at whole need for resources like this.

DOCTOR COOK-DEEGAN: Is that the ROWE Committee?

DOCTOR KIRSCHSTEIN: Yes.

DOCTOR COOK-DEEGAN: Okay. Is there anything that we need to do to gather information or the mechanisms that we could use to try to gather information cheaply and rapidly?

DOCTOR KIRSCHSTEIN: No.

DOCTOR COOK-DEEGAN: Okay.

CHAIRMAN LOWRANCE: Other projects, LeRoy?

DOCTOR WALTERS: It seems as if we have a national policy on patents and copyrights, but trade secrets are a state matter. Without wanting to intrude on the federal/state relationship, I'm wondering whether some kind of guidance, or at least some kind of active study of the question of a national policy on trade secrets might be useful.

DOCTOR COOK-DEEGAN: Susan, do you have any comments on that? I don't even know what that would mean.

DOCTOR COZZENS: I guess it would be helpful to know what particular issues you would want to focus on that. In other words, what kind of problems do you anticipate with respect to trade secrets that you think might warrant examining national legislation?

DOCTOR WALTERS: Well, I'm not sure it would be national legislation, but it seems as if every group has to work out a kind of ad hoc policy

and a set of bilateral arrangements for disclosing information that otherwise would be retained as a trade secret. Maybe there are problems that span various fields and maybe something like a proposed model law from commissioners that develop model laws for their states would be useful in this arena, if trade secret information is of great importance in this area as well as other areas.

DOCTOR COOK-DEEGAN: Or perhaps it would be simpler to look at what some of these collaborative agreements look like and see if we could come up with a model for something like that.

CHAIRMAN LOWRANCE: We have a comment from an observer.

Would you introduce yourself?

MR. WILLIAMS: Sure. I'm Jack Williams. I head up something called the Office of Productivity Technology Innovation in the Congress Department.

Bob, a couple data points for you. Number one, the Administration is reviewing this, the science and technology agreements with other countries. One of the points of interest is, who

owns the technology which is developed under a collaborative project? For example, with Japanese scientists and American scientists. There is no policy on that at this time. Some of the folks referred to the fact that there were something like 300 Japanese scientists at NIH and 12 U.S. scientists, that type of thing. So, that's an evolving issue.

Secondly, Susan knows this better than I do, it's called the Dole Amendment, I guess it is, for technology transfer patents. This gives federal laboratory directors the power the refuse access by foreigners into their laboratories. Reciprocal access is afforded to our scientists abroad so there's a constraint there, which you might want to think about.

CHAIRMAN LOWRANCE: Thank you.

Any other comments from the other observers or questions?

Other nominations for OTA's work in the next couple of months? I say that because you're headed toward a fall deadline in general.

DOCTOR COOK-DEEGAN: I guess the message I'm getting is, go to your word processor and start typing. That's fine.

CHAIRMAN LOWRANCE: Any closing comments on the day in general?

I think Bob, just a moment ago, mentioned a couple of the key themes on the legal side and the repository issue.

Susan?

MS. ROSENFELD: What would be helpful to me, to get a sense if there's been any narrowing of the issues that you would like us to address. It seems that there's a great interest in having us focus on the copyright issue or maybe that has gone away. I don't know.

CHAIRMAN LOWRANCE: Just settle it.

MS. ROSENFELD: But what I read through this morning was a rather extensive list and I think from just a practical point of view, given the time frame by which something needs to be written out of that whole list, some decisions are going to have to be made as to which issues we should be focusing on.

DOCTOR STEPHENSON: Were any issues identified? It seems to me that in that whole area of patents and so forth, that the issues which were put up were not down rather promptly and then basically the legislation, the regulations, the mechanism for review and evaluation are all in place and that nobody could identify anything that was peculiar about this stuff which wasn't also the subject of the same regulations in biotechnology or conventional type material.

MS. ROSENFELD: I think that some of the kinds of things that might be looked at, and perhaps I wasn't that clear this morning, would be to take a further look at some of the potential applications and limitations on the applications of the various pieces of federal legislation which govern the ability of government grantees to dispose of and acquire proprietary rights in inventions made with federal funds.

What I did was refer to certain provisions in the legislation, for example march-in rights, which set certain criteria which need to be met in

order for the government to come in and either take back rights and inventions which have been given to the private sector or require that those rights be made available to third parties in the private sector.

One of the questions would be that those statutory provisions are written in very general terms. The question would be, how would those general provisions apply to a specific project of this nature? What kinds of situations would they apply in? For example, there is a provision that I referred to where if there are certain health and safety needs that are found, you can have march-in rights.

But the question is, what kind of a situation would meet the statutory criteria of a health and safety need? It wouldn't be what everybody thought of as a health and safety need. It's got to have a more specific meaning and what might be useful would be to try and defined further, based on the legislative history, based on comparable situations elsewhere, based on other governmental

regulations affecting contracts with the private sector to see if any further standards could be specified on that.

DOCTOR STEPHENSON: All of these things are interesting speculation. Do you know of any case actually where a case law has settled any of these issues or the issues have even been adjudicated?

DOCTOR COOK-DEEGAN: Do we even know of any cases where they've been used, march-in rights have ever been used?

MR. GOULD: The threat of a march-in I think was used in the extension of an anti-cancer drug where they were able to extract a lower price from the seller as a result of an extension of the exclusivity. So, I think in that one instance, the government did threaten and exact out some accommodation from the licensee.

CHAIRMAN LOWRANCE: LeRoy?

DOCTOR WALTERS: I think as a complement to the legal focus, it would be useful to come back to a point that Jim Childress raised this morning. What values is one seeking to promote?

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CHAIRMAN LOWRANCE: LeRoy?

DOCTOR WALTERS: I think as a complement to the legal focus, it would be useful to come back to a point that Jim Childress raised this morning. What values is one seeking to promote?

I can see values at different levels, at the level of a commercial firm and its shareholders to have certain values that are being promoted, at the level of the nation and then there are also, I think, more universal values like contribution to knowledge or a contribution to the conquest of disease. Once you set those values out, then you can look at the law in terms of whether it's instrumental in achieving those values or whether, in some ways, it inhibits achieving those values. It just gives it a different perspective on the law.

CHAIRMAN LOWRANCE: Ms. Cozzens?

DOCTOR COZZENS: But the impression that I would have from our discussion is that there's general agreement that all of those interests are served the more information sharing you have. The more things that are held secret, then the worse off commercial interests are, scientific interests, human interests, all of the ones that you just ran through.

So, the task is really the one that Bob set out initially, which is how can the legal structure minimize holding information secret and not putting

it into public access in one form or another?

Once again, from listening to the whole discussion, the impression that I have is that the better the traditional mechanisms for doing that work in this circumstance, the fewer secrets you're going to have, whether it's professional secrets held by scientists or secrets held within private firms. The better the patent regulations work, the more patentable these various inventions are, then the more people are going to go ahead into the patent process and put the information into public domain, or at least the parts that aren't of clear commercial interest.

So, I would say the question in terms of which legal issues to focus on, I would run through this list of possible results of the genome project that's been so comprehensibly drawn up and say, "All right, are there places here where those traditional protections are weak?" And if so, those are the places to focus on. How can we make the traditional protections stronger or clarify the situation in a way that everybody feels comfortable with bringing

out all of the information that they can actually bring out.

There's going to be some residue of things that people will never talk about, no matter what the legal framework is. But the task seems to be clarifying and putting as much as that information into the "we all feel comfortable about sharing it realm" as possible.

DOCTOR KIRSCHSTEIN: Which I think, in point of fact, is what's been happening, at least in our situation over the years. If anything, we have loosened regulations, interpreted law as broadly as possible and, in fact, it's what the Commerce Department has encouraged everybody to do. So, I would hope that you wouldn't do anything that would look like it's going to try to constrain again, which is what I think Bob was getting at.

DOCTOR STEPHENSON: Yes. And also, all of your comments are not only true at the national level, but also internationally because if people are fearful that other countries not signatory to patent treaties don't respect your proprietary rights and so

forth, then people will hold back because they figure, "Well, okay, I can protect it here, but I can't protect it in Korea or I can't protect it in Taiwan. And once this gets out, they'll run off to the races with my invention.

CHAIRMAN LOWRANCE: Mr. Karny?

MR. KARNY: I think one thing that will be of use in Susan's work and in the OTA work will be simply educating the people as to the nature of a lot of these rights and what they do and do not involve. A lot of this discussion did come up in the early days of the recombinant DNA work and there was a lot of fear that work would be stopped, information would not be shared and so forth. I don't think that's been the case.

I had heard a lot of concern about people locking up E. coli genome and I think what we have here, to a certain extent, is a new group of scientists, and Bob alluded to it early today when I asked him what is the driving force here, who are running up against a new area and being concerned about how this will affect their work. Of course,

that is a serious and valid concern.

I think there may be instances, obviously, where it will or it could. But I think a discussion, clarification, of some of these basic concepts at least will dispel some of the concern and perhaps then serve as a basis for further discussion. I have the feeling this OTA report will not be the last word in this area. It's going to be an evolutionary --

DOCTOR COOK-DEEGAN: It's certainly not the first.

MR. KARNY: -- evolutionary debate. I think that sounds pretty basic, but I still think that will be useful.

CHAIRMAN LOWRANCE: Other general comments?

MR. GOULD: I found one specific clause in Susan's remarks that would cause me some concern as being a disincentive to engage in a collaborative program. That would be on page 10, paragraph 4. That's the so-called "background rights" problem with government contracting where, based on a determination under a very ambiguous standard, the government agency would have the right to obtain a

license on patents that the contractor owned which were not generated out of the government funding and merely exact a license out of that if there is a presumed need to carry out some of the purposes of the project.

So, I think that's a danger and I think any commercial organization would, if they would try to put such a provision in, would certainly want to resist the -- or would be quite sensitive to it. I think what we were saying before in terms of policy was that we were trying to build in incentives to get industry and government to collaborate.

Since this is a permissive part of the statute, there's no obligation to do so. It merely permits the agency that OTA would take the stand that such would be a disincentive and therefore should not be considered. That might be a very positive step in the kind of program we're talking about.

MS. ROSENFELD: Let me just say, the way in which I structured my comments was essentially to assume that there could be situations where people might not voluntarily want to cooperate, either in a

limited way involving just individual investigators or for some reason on a broader basis. Then, making that assumption, I tried to address some ways in which one -- some of the remedies that might be available to resolve that problem.

My general sense from the group is that nobody believes that that type of scenario is likely to arise. You certainly know better than I. I guess I just sort of wonder, in a situation where you have many, many collaborators, both individually and institutionally coming from many different points of view, government, industry, universities, whether or not one can assume that you're not going to have problems where people -- maybe not today, but during the course of this kind of project -- might decide, for whatever reason, that at that point they want to stop collaborating in terms of exchange.

I guess if it looks like there could be that likelihood, that's what a lot of these issues are really meant to address that possibility.

The other comment I want to make is really related to something that Doctor Kingsbury said,

which has to do with the legal authority of the federal government to impose certain conditions in funding agreements enter into under this particular project.

He mentioned that the general counsel of his agency had had some reservations with respect to the databases accumulated in the social services area. There may very well be comparable or even greater problems relating to areas where patents may be involved. I touched briefly on that earlier in my comments. Again, that may be an issue which might be worth taking a look at, since presumably these agreements will be entered into at the beginning of a project and will be in existence for a significant time period thereafter. Whatever problems are going to come up are going to come up under these agreements.

So, I raise that.

CHAIRMAN LOWRANCE: Thank you.

Any concluding general comments? Mr. Karny, are you responding to this?

MR. KARNY: Just two follow-up comments.

First, I notice one of the things on the agenda was this idea of a multicenter approach. We obviously didn't talk too much about that. I think it's an intriguing idea. Again, it could be a difficult and very amorphous area to grab hold of, but you might consider doing some work on the concept of how you could bring people together in a center, the private and public sector, and what type of contractual arrangements could be negotiated in terms of ownership and sharing of information.

Maybe that's a whole project in and of itself, I don't know, but I think it's an interesting idea. You might give it some initial thought to whether it's worth doing anything more there.

Just a second quick point. One thing that I hope is clear in the report when we're talking about what, in any, limits should be put on patents and property rights and so forth is the distinction between patents that have originated from entirely private work and privately funded work and those which originate from publicly funded work. And I think it clearly is a distinction there.

There are stronger arguments to be made that one could limit the rights -- government could limit patent rights if it's funding the project. I have a lot of problems with arguments that patent rights of a private nature ought to somehow be limited or taken away unless we've got some type of eminent domain procedure.

DOCTOR ALFORD: That's an interesting thing, but I think if this project were to succeed and I think in a fashion we addressed multicenter collaboration but differently, that we're going to share information maybe through database or through repositories.

If there is a way to share such information, which we're going to have to be able to do, and still protect one's proprietary rights, I think it's a non-issue whether that patent will be generated by private industry monies or by federal monies. I want to be able to share my private industry patents information with others and I don't think there will be any restriction as long as there's some protection that I could be given for my

proprietary information and so that someone won't use it.

MR. KARNY: In the concept of a center, that's fine. Also in terms of some type of voluntary arrangement or incentive. Maybe I'm being overly concerned about a small area, but one thing I am concerned about is some finding, discussion, whatnot, in terms of somehow, because the human genome is so special and that conquest of disease is so special that private patent rights ought to somehow be taken by government fiat or limited by government fiat.

We didn't talk a lot about that today, but that is something of an undercurrent, at least for some of this. If you're going to get into that area, I think you just have to be very careful of the distinctions being made so when your arguments are put forth, it's clear what you're talking about. Talking about limiting patent rights when you're talking about federally funded may cause people less concern. Whereas if it's entirely private rights, then I think there are other considerations.

CHAIRMAN LOWRANCE: Doctor Kirschstein?

DOCTOR KIRSCHSTEIN: But in point of fact, it works quite the opposite way and I hope you would stress that. In point of fact, what the government has done is to provide private patent rights to organizations that it supports the research of. The recombinant DNA technology patent rights are residing at Stanford for which the government put up the entire set of --

MR. KARNY: I'm very well aware of that.

DOCTOR KIRSCHSTEIN: Yes, I know. But the point is that the government is doing it the other way. So I don't think you really have to worry about that. I think you're being overly concerned.

MR. KARNY: Okay. Maybe I'm being concerned about something that is, by this point, at non-issue. But it's just -- we haven't made the distinction all day between the entirely private rights and rights arising from federally funded research and I just think in certain areas that a distinction is appropriate.

CHAIRMAN LOWRANCE: I suggest that we draw ourselves to a conclusion while we still have some

energy. We've touched on a lot today. As Chairman for a day, I'd like to thank the group and say I hope that if you have afterthoughts after the meeting, that you will telephone Bob or Susan and help them shape up their studies. They have an enormous task left to do, whereas we all get to go home. So, if you do have afterthoughts, please send them in or telephone them.

Bob, do you have any concluding --

DOCTOR COOK-DEEGAN: No. I just want to thank everybody for coming. I think it's been extremely helpful for us. I think all of our objectives have been met for today.

Just to warn you a little bit, several people who have raised points, when we get the transcripts back, you probably won't have enough information to fill the gaps for the purposes of writing the reports. You can expect some phone calls to figure out details here and there and get references and that sort of thing.

But thank you so much for coming and sharing your time and energies with us.

(Whereupon, at 3:44 p.m., the meeting was concluded.)

C E R T I F I C A T E

This is to certify that the foregoing transcript

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represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Kyle Ono
Reporter